

The Value of Ignorance: Antidepressant Drugs and the Politics of Objectivity in Medicine

Linsey McGoey

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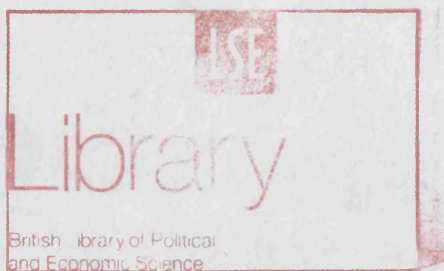


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Abstract

This thesis explores the strategies of ignorance and uncertainty employed by UK regulators, practitioners and policymakers during the controversy over whether selective serotonin reuptake inhibitor (SSRI) antidepressants such as Prozac contribute to suicidal and homicidal reactions in some users. Empirically, the thesis is based on archival research, textual analysis, and interviews with UK policymakers and clinicians involved with efforts to determine the safety of SSRIs. By analyzing these materials with methodological and conceptual tools from the fields of science studies and the sociology of reason and objectivity, the thesis demonstrates the following four findings.

First, drawing on the case of SSRIs, I demonstrate that many policymakers within the UK's National Health Service are frustrated with their inability to access clinical trial data necessary for developing treatment guidelines. Second, I argue that problems surrounding access to clinical trial data illustrate weaknesses within evidence-based medicine, a model of medicine that has become dominant in the UK and internationally over the past three decades. Third, I argue that when practitioners and policymakers wish to criticize the socio-political factors that make it difficult to access clinical trial data, their dissent must be limited to the universe of numbers, a phenomena which I term the "moral authority of objectivity" in medicine. Fourth, drawing on interviews with expert advisors to the MHRA, I argue that, in the case of SSRIs, regulators employed a strategic use of ignorance in order to absolve themselves of liability in not disclosing the knowledge of adverse effects when they first learned of them. This final finding has theoretical implications for recent studies of uncertainty and ignorance. I suggest that the SSRI controversy illuminates the regulatory value of inconsistent, uncertain and contradictory facts. The usefulness of uncertainty lies in its performative nature: uncertainty creates a demand for solutions to the ambiguity which it perpetuates, often consolidating the authority of those who have advanced a position of uncertainty to begin with.

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Chapter One: Introduction

Few concepts have attained as much rhetorical authority and political value in recent years as that of evidence. With its inception in the evidence-based medicine movement that has emerged in just a few decades, the term “evidence-based” has become a much employed qualifier, favoured by politicians and policymakers alike in order to offer legitimacy to a phenomenon, from “evidence-based economics” (Berg 1995; Porter 1995; Reiss 2007) to “evidence-based law” (Adshead 2003), to even “evidence-based chaplaincy” (O'Connor 2002).

On its own, the concept of evidence-based medicine is fairly narrow in its scope, intended to encapsulate the advantages of basing medical treatments on the best available scientific evidence, preferably in the form of randomized controlled trial (RCT) data (Sackett 1996). From its roots in this modest conception, the term “evidence-based” has become a leading concept in medicine and politics, where evidence-based policies are seen as a safeguard against partisan or vested interests. In policy circles, for example, the concept of evidence has been vital, as William Davies notes, to British politics throughout New Labour’s tenure in office – a crucial complement to the “what matters is what works” mantra employed by ministers outspoken in their goal to keep “ideology at bay” from politics (Davies 2005).

To many, the recent adoption of “evidence-based” methods in both health care and politics is seen as the logical extension of the centuries-long effort to adopt systems of governance based on rational, scientific forms of reasoning. Historically, well-meaning observers on either end of the political spectrum have sought to build a “science of politics” in the UK and internationally, where decisions are based more

on evidence and less on the vagaries of personal status or opinion. British socialists Beatrice and Sydney Webb were outspoken in this goal, suggesting that a politics based less on ideological whim or partisan courtship and more on scientific evidence would create more equality in Britain (see, for example, Letwin 1965). From a more conservative perspective, Alexis de Tocqueville proposed a “new science of politics” as a way of controlling the more nefarious implications of the adoption of democracy in America, of curbing what he saw as democracy’s erosion of individuality and political engagement (Tocqueville 1848; Offe 2005). In the mid-20th-century, Michael Polanyi suggested the move to a “republic of science” would create more open and transparent politics based on reasoned decision-making and not populist courtship (Polanyi 1962).

The hopes of these authors have long been questioned by scholars in government studies, philosophy, science studies and other fields who have suggested that a “science of politics” is a contradiction in terms. Not only, they suggest, is it impossible to eradicate subjectivity, emotions and populist sentiments from political arenas, but science itself is beset by subjective phenomena. As the oft-heard refrain goes, politics are everywhere, including the domains of science and medicine, and because science is in part politically manufactured, the ideal of importing scientific impartiality and disinterestedness to politics is an elusive one. In this vein, critics scorn the effort to introduce more scientific rigour to medicine, and suggest that the “evidence-based” methods underlying EBM should be viewed as all the more pernicious for purporting to be free of ideological influences (see, for example, Holmes and colleagues, who suggest evidence-based medicine is an example of “microfascism ” (2006).

In this thesis I draw on a case-study analysis of the controversy over selective serotonin reuptake inhibitor antidepressants (SSRIs) in order to assert that such critics are, if not mistaken, then at least short-sighted. Andrew Barry has recently suggested that, against the common sociological view that politics can be found in all variety of economic and social arenas, politics is actually “a rather specialist activity,” contingent not on a diverse and plural range of actors, but to an ever-narrowing field of experts and advisors capable of arbitrating on technical and instrumental matters (Barry 2002: 268).

Drawing on this insight, I suggest that EBM is, in contrast to the rhetoric of its most adamant critics, a markedly *depoliticizing* phenomenon, remarkable not for its political implications, but for its lack of them. EBM has not rendered it more possible for practitioners to challenge the “eminence” of superiors, or to contest, as this will show, regulatory decisions on the safety of a given pharmaceutical product. If, as critics suggest, the ideals of EBM are illusory, then they are practical illusions with very real consequences – one of which has been to narrow the scope of contestation available to those living under the rubric of increasingly science-based policies.

In tandem with the argument that the SSRI controversy reveals the depolitical nature of evidence-based medicine, I explore something that has received relatively little attention in the sociology of medicine: the value of ignorance and uncertainty in helping a range of parties, from clinicians to regulators, to secure authority in debates over the safety of pharmaceutical drugs. At first glance, the discussion of uncertainty throughout this thesis is hardly novel. Efforts to manage scientific uncertainty have of course long been a concern of scientists, philosophers and sociologists of science (Hacking 1990; Gigerenzer 1995; Gigerenzer 2002). What has received less

attention, however, is the value and usefulness of uncertainty: its commercial value in fostering productive doubt over the safety of a product, its regulatory value in legitimating past actions, and its political value in securing funding and support for a particular course of action. Only recently have scholars started to scrutinize the emergence of actors who employ their own “fear of uncertainty as a resource” (Thrift 2005: x).

Drawing on work by Niklas Luhmann and Michael Power, I suggest that a “politics of conditionality” has emerged in recent years, where the complexity and contradictions inherent in competing scientific facts are increasingly employed as a form of political capital. Recently, those with political or cultural authority have grasped that uncertainty provides a reprieve from having to answer for the consequences of one’s knowledge. Conditionality and uncertainty are often more advantageous rhetorical tools than certainty: one can not be held accountable for what one could not have known. The prevalence and influence of uncertainty can be seen in a wide range of phenomena, from the introduction of the precautionary principle to regulatory policies, to the deliberate use of scientific inconsistencies by the victims of ecological or chemical disasters in order to contest bureaucratic assessments of harm (see Das 1995; Petryna 2002).

At first, it seems apparent that the concepts of “evidence” and “uncertainty” are opposite resources, with the assertion of one cancelling the possibility of the other. As “evidence” is a term routinely deployed by those *with* authority, be it scientific, political or both, it seems only logical that uncertainty, the antithesis of evidence – would be a resource of those *without* political or scientific clout. Particularly in today’s liberal societies, where few political goals are valued as much as the ideal of basing political and technical decisions on rational, scientifically rigorous evidence,

pointing out that an expert lacks requisite scientific certitude seems the 21st-century correlate to exposing the Emperor's lack of clothing. In principle, then, it seems apparent that the admission of uncertainty is a liability for those who hold scientific authority, and a source of power for those who don't.

In practice this is not the case. Drawing on the controversy over the safety of SSRIs, I demonstrate that both scientific evidence *and* scientific uncertainty were mobilized by government regulators in order to absolve them of the failure to act swiftly in response to the recognition of the adverse effects of SSRIs. Secondly, I suggest that, as a result of what I term the "moral authority of objectivity," everyday practitioners have been unable to contest assertions of both scientific certainty and uncertainty unless they have the institutional capital to, as science studies scholar Brian Balmer puts it, express "legitimate doubt" (Balmer 2006). I demonstrate these arguments by drawing on interview data with psychiatrists and policymakers involved with the recent effort to determine the safety of SSRIs, one of the most profitable classes of drugs ever produced.

SSRIs were first marketed in the United States and Britain in the late 1980s. The all-time bestselling SSRI is Eli Lilly's Prozac, which saw its patent expire in 2001. In the years leading up to its patent expiration, Prozac generated approximately \$2.6 billion for Eli Lilly annually, a full quarter of the company's total revenues (Shook 2000). A recent article in Fortune magazine notes that "Prozac and its kin have been one of 20th-century medicine's great success stories. Since the debut of Eli Lilly's Prozac in 1988, the drugs have grown into an \$11-billion-a-year market in the US alone. Nearly 150 million US prescriptions were dispensed in 2004 for SSRIs and similar antidepressants called SNRIs...more than for any other drug except codeine. Perhaps one out of 20 adult Americans are on them now, making brands

like Zoloft, GlaxoSmithKline's Paxil, Forest Laboratories' Celexa, and Solvay Pharmaceuticals' Luvox household names" (Stipp 2005).

Despite their popularity, a number of psychiatrists and consumers have recently raised concerns about the safety and the efficacy of the drugs, particularly in relation to the question of whether or not they lead to suicidal reactions in some users. Drawing on in-depth interviews with individuals involved with efforts to determine the safety of SSRIs, this thesis demonstrates the following main findings:

- 1) The controversy over SSRIs has drawn attention to the fact that, across many areas of medicine, UK policymakers who are responsible for formulating clinical guidelines on the safety and effectiveness of medical treatments do not have adequate access to the clinical trial data necessary for forming their opinions.
- 2) As clinical trials are the dominant technology for determining a medicine's safety within EBM, I argue the controversy over the safety of antidepressants illuminates a number of weaknesses within the EBM model. A central principle of EBM is that the use of evidence from large-scale RCTs in the guidance of clinical actions will help to minimize clinical variance and result in higher standards of health care. Contrary to such an expectation, the controversy over antidepressants has emerged despite the widespread availability of clinical trials assessing their risk-benefit profile. Its emergence therefore raises questions about the design, publication and interpretation of clinical trials in general.
- 3) Even though medical practitioners often recognize – and at times resent – that commercial factors make it difficult to access clinical trial data, a phenomena which I term the “moral authority of objectivity” demands their dissent is limited to the universe of numbers.
- 4) Government regulators at the Medicines and Healthcare products Regulatory Agency (MHRA) employed a strategic use of ignorance in order to absolve themselves of liability in not disclosing the knowledge of adverse effects when they first learned of them. This final finding illustrates the value of inconsistent, uncertain and contradictory facts. It demonstrates that uncertainty is performative: it creates a demand for solutions to the ambiguity which it perpetuates, therefore consolidating the authority of those who have advanced a position of uncertainty to begin with.

Synopses of chapters

Chapter 2: Methods and Literature Review

Methodologically, this thesis is based on archival research, textual analysis, and a mixture of both formally structured and informal interviews with policymakers and clinicians involved with efforts to determine the safety of SSRIs. In this chapter, I discuss these methods in more depth, and describe the three areas where the thesis makes contributions to the sociological literature: Firstly, to the literature on the social construction and regulation of randomized controlled trials. Secondly, to literature on the social implications of evidence-based medicine, which I link to a discussion of the social and political consequences and implications of claims to objectivity within medicine. Thirdly, to literature within sociology and science studies on the productive value of ignorance and uncertainty.

Chapter 3: Drugs regulation and the politics of objectivity in medicine

In Chapter Three, I explore the rise of evidence-based medicine in Britain, a model of medicine which has emerged over the past four decades. The term itself was coined in 1992 by a group of clinical epidemiologists working out of McMaster University in Hamilton, Canada who criticized clinical decision-making based on individual experience as an out-of-date paradigm and who sought to develop a system of assessing the risk and benefits of drugs which would apply statistical probability theory to clinical decision-making practices (Mykhalovskiy and Weir 2004).

The epidemiologists working in McMaster were aware of the work by Archie Cochrane, who had suggested two decades earlier that there needed to be more

systematic measures to verify whether existent medical treatments were effective (Cochrane 1972). Cochrane called for the establishment of an international register of randomized controlled trials and for open and transparent criteria for appraising the validity of published medical research, a goal which has been enshrined through the establishment of the Cochrane Collaboration, an organization dedicated to providing public access to syntheses of both quantitative and qualitative research on health outcomes.

In the chapter, I discuss the emergence of EBM in relation to the growth of the pharmaceutical industry in Britain, exploring the industry's evolving relationship with the MHRA, the main government body responsible for drugs regulation in the UK. Since 1989, the MHRA has been 100% funded by fees paid to the regulator by industry in exchange for licensing its products. Though the reliance on industry funding is not unusual in comparison to other European drug regulators, a number of the practitioners I spoke to expressed concerns with the MHRA's funding structure. Despite the fact that they voiced concerns privately in interviews, many also noted that they felt hindered from publicly acting on their resentment and mistrust of industry.

Their concerns pointed to a number of contradictions with the EBM movement. There is an assumption among some advocates that organizations such as the Cochrane Collaboration have fostered greater transparency and access to information. I argue, however, that such a claim ignores the *current* economic and political constraints which affect the validity of all evidence that finds its way to places such as the Cochrane. Many advocates ignore, for example, that most clinical trial data is funded by companies that are not mandated to publicly disclose all clinical trial data relevant to a treatment.

At times, it has been EBM proponents themselves who have been most vocal about the political and commercial factors making it hard to access RCT data. Iain Chalmers, for example, one of the founders of the UK Cochrane Collaboration, has struggled for over two decades to draw more attention to problems of “publication bias,” or the deliberate non-disclosure of clinical trials where a drug is shown to be inefficacious or unsafe (Chalmers 1990; Chalmers 2006). Although a minority of EBM proponents such as Chalmers have been outspoken in voicing resentment of industry tactics, among others I found an unwillingness to discuss the ways that industry censorship of RCTs might influence the quality of evidence that finds its way to places such as the Cochrane. A paradox emerges: as advocates of evidence-based medicine, a movement which espouses the aim of freeing medical evidence of subjective bias, why are proponents, barring a few exceptions, reluctant to discuss or to contest overt commercial bias?

Drawing in part on Theodore Porter’s argument that progress in science is reliant on the “exclusion of judgment, the struggle against subjectivity” (Porter 1995: ix), I argue the authority of objectivity in medicine hinders practitioners from voicing critiques of the political and commercial influences on their profession, unless their objections are clothed in the language of numbers.

Chapter 4: SSSIs, suicide and the use of strategic ignorance at the MHRA

In this chapter, I map the specificities of the controversy over the safety of SSRI antidepressants. I introduce the main actors – such as psychiatrists, psychopharmacologists, epidemiologists, clinicians, government regulators, pharmaceutical companies and patients groups – who have been central to the controversy’s emergence and trajectory, and explore the main factors – political,

social and economic – that have contributed to the scale, level of animosity, and irresolution of the controversy.

I then suggest that a key factor leading to the lack of clear answers regarding the risks and benefits of SSRIs is the onus on regulators to act in accordance with something which I term “anti-strategies,” or the tacit interests at root in any regulatory process, inquiry or hearing which works to contradict the outspoken goals of the inquiry. In the case of the MHRA’s many inquiries into SSRI, the anti-strategy was two-fold. Firstly, the commercial need to maintain positive relations with the pharmaceutical industry funding the MHRA’s operations. Secondly, the need to retain public trust in the agency’s competency. Those two demands circumvented the MHRA’s ability to carry out its explicit goal: arbitrating on the safety of drugs and removing from the market any drugs indicated to carry more risks than benefits.

Finally, I argue, drawing on work by Nietzsche and Luhmann, as well as data from interviews with individuals such as Kent Woods, CEO of the MHRA, and Richard Brook, a former expert advisor to the MHRA, that a purposeful “will to ignorance” was employed by regulators in order to absolve themselves of the failure to act swiftly when evidence of the adverse effects of SSRIs first appeared.

Chapter 5: Regulatory battles: The politics of transparency and disclosure within NICE and the MHRA

This chapter looks in more depth at questions surrounding the design, implementation and dissemination of the key technology for determining drug safety within EBM: the randomized controlled trial. Firstly, I provide a history of the introduction of the RCT to medicine. Secondly, I examine a number of factors that can affect the validity of trial results, leading to competing and conflicting interpretations of the same clinical trials.

Thirdly, I suggest that for many practitioners, much anger and concern has stemmed from the growing awareness that some pharmaceutical companies have purposefully manipulated RCT data to suit their commercial purposes. For many, the revelation of industry tampering in the SSRI case was one of the first times that belief in RCTs as yielding “pure” scientific evidence was lost. I suggest that this loss of faith in the evidence of RCTs may have been compounded by the fact that many medical practitioners are guided by what Nikolas Rose has called a “morality of numbers,” where “impersonality rather than status, wisdom or experiences becomes the measure of truth” (Rose 1999: 208). I discuss the various strategies used by practitioners to make sense of their personal perceptions of the safety of SSRI in the absence of conclusive scientific evidence.

In particular, I explore the finding that, despite their realization of the political nature of many medical decisions, many practitioners feel powerless to voice their own resentment unless they had recourse to RCT evidence that could justify their objections. This observation relates, I suggest, to work from Pierre Bourdieu on the genesis and cultural reproduction of state authority. In “Rethinking the State: genesis and structure of the bureaucratic field,” Bourdieu has argued that state injunctions owe their obviousness, and thus their potency, to the fact that the state has sought to impose the very cognitive structures through which it is perceived. He suggests that people respond doxically, or pre-reflexively, to a social world riddled with “calls to order,” and argues this pre-reflexive submission helps to explain the ease with which the state maintains its monopoly over physical and symbolic violence (Bourdieu 1999: 69).

From this insight of Bourdieu’s, I take a simple but powerful point. It is within the nature of any authoritative power to influence and prescribe even the forms of

resistance which that authority has engendered in the first place. In the case of medicine and science, internal critiques, to garner any credibility, are often forced to appropriate the methods of those whom one wishes to oppose. Thus an invulnerability of method emerges, something which I term “methodological mimesis.” The mimetic power of dominant methodologies can be compared to what Power has called the “opacity of process” (Power 1994). Power stresses that a curiosity of the financial audit is that in times of financial breakdown, such as during accounting scandals, belief in the audit as a policing mechanism becomes even more entrenched. Calls are heard for more audits, and very rarely for an analysis of how the detection process was flawed in the first place. I argue that RCTs share with the audit this apparent methodological invulnerability.

Finally, the chapter stresses that the lack of certainty over the safety of SSRIs is not particular to this class of drugs, but points instead to problems surrounding the design, publication and implementation of RCTs in general.

Chapter 6: The moral authority of randomized controlled trials

In this chapter I suggest that RCTs can be conceptualized as form of inscription devices, or phenomena that rally support in an antagonistic situation. Bruno Latour notes that the “essential characteristic of inscriptions cannot be defined in terms of visualization, print and writing. In other words, it is not perception that is at stake, [but] that of mobilization” (Latour 1986: 7). A number of sociologists have applied Latour’s argument of the rhetorical function of inscriptions to the realm of numbers. Rose, for example, notes that “numbers, like ‘other inscriptions,’ actually constitute the domains they appear to represent; they render them representable in a docile form – a form amenable to the application of calculation and deliberation” (Rose 1999:

198). In the chapter, I apply the work of Latour and Rose to RCTs, arguing that it is the ability of RCTs to render complex medical information more accessible to physicians that can help account for their growing pervasiveness as the dominant methodology in drug development and in health care generally.

My final claim in this chapter draws on work by Jack Goody on literacy. Comparing RCTs to Goody's argument in the essay "What's in a List?" (Goody 1977). I argue that a shortcoming in the work of both Latour and Goody is their belief in the process of transcription as a politically enabling phenomenon.

Chapter 7: The Consolations of Chaos: The performative nature of uncertainty

In Chapter Seven, I explore one of the leading causes of the lack of resolution to the SSRI controversy: problems surrounding the withholding of clinical trial data on a given drug or treatment from government policymakers and the public. Firstly, I compare the SSRI example to the case of Merck's Vioxx, the anti-inflammatory drug removed from the US market in 2004 after evidence emerged of the drug's implication in cardiac failure in some users. I then point out, drawing on the case of the SSRI and Merck, as well as work by Andrew Barry and George Simmel on the reciprocal nature of secrecy and disclosure, some of the shortcomings in the typical public and media responses to the recent series of drug scandals involving the withholding of clinical trial information from regulators and policymakers. That response has generally been to demand ever more intricate forms of regulation and more disclosure of clinical trial information. Insufficient attention is paid, as Bridget Hutter and Michael Power have discussed in relation to Enron and 9/11, to the institutional conditions that render it difficult for actors to act on evidence of

problematic behaviour even when information is fully disclosed (Hutter and Power 2005).

Finally, drawing parallels between the cases of Enron, Vioxx and SSRIs, I suggest that a purposeful use of uncertainty has been a key resource to manufacturers and regulators in deflecting blame for earlier misconduct or mistakes.

Chapter Two: Study design, methods and literature review

Research questions and methodology

This study has employed a combination of archival research, textual analysis and interviews conducted with expert sources, such as consultant psychiatrists, policymakers, epidemiologists and regulators, who have been involved with efforts to determine the safety of SSRIs.

Prior to conducting my research, I had posed the following research questions: To what extent have estimations of moral character been central to the debates over the safety of SSRIs? Has it been the case that knowledge of the tenuousness of one's professional standing, and the effort to win accreditation from one's peers, have played a part in various regulatory decisions over SSRIs? How do these questions over SSRIs relate to the growing paradigm of evidence-based medicine? The decision to explore the narratives, perceptions and professional disputes among individuals central to the public debates over SSRIs was guided in part by two key texts: anthropologist Paul Rabinow's *Making PCR: A Story of Biotechnology* (1996), and historian and social theorist Steven Shapin's *A Social History of Truth* (1994).

In *Making PCR*, Rabinow describes the founding of a biotechnology company in California. The bulk of his analysis consists of detailed expositions of the biographies of the founders of the company, which was developed in order to bring to market a major new scientific discovery: polymerase chain reaction, the technology necessary for the decoding of DNA. Rabinow illustrates how the subjectivities of key players – the desire for self-gain, the perception of one's peers – were central to the development of the technology of PCR as a groundbreaking

scientific discovery. Throughout the book, Rabinow employs a flexible and inductive style of interviewing, aimed at soliciting biographical details from his informants, as well as their subjective opinions on the motives, aims and goals for working in biotechnology. The theoretical impetus behind this focus on subjectivity is not, as has sometimes been suggested of Rabinow, the assertion of strict epistemological relativism which suggests that because all truths, including the discovery are new scientific entities, are in part socially constructed, it renders those truths incommensurate. Rather, it is guided by Rabinow's recognition, in *Making PCR* and in the writings described below, of the importance of individual perspectives in the production of which truths, in any given period, individuals chose to place faith in and adhere to.

In *Anthropos Today* (2003), Rabinow draws on sources such as Weber's "Objectivity in Social Science and Social Policy" (1904) and "Science as a Vocation (1918)", and Foucault's *The Order of Things* (1973), to make two points relevant to the discussion of methodology in this chapter. The first is the fruitfulness of focusing attention on concrete, empirical, and identifiable phenomena. The second is the recognition that perceptions of phenomena are always constituted through specific historical and discursive relations.

For support of the first point, he turns to the discussion of the goals of social science in Weber's work. He notes that for Weber, the "type of social science in which we are interested is an empirical science of concrete reality....our aim is the understanding of the characteristic uniqueness of the reality in which we move," and then asks, how does Weber manage to apprehend and analyze the characteristics of shifting, changing realities? His response is that Weber manages this through a focus on the singularity of any given situation:

Weber's view is not one that claims to grasp total patterns of life understood as organized wholes. Weber and his colleagues are not Clifford Geertz reading the text of Balinese culture, leaning over the shoulders of the Balinese, who are, as Geertz believed, enacting it for him and for themselves. Rather, the Weberian position is historical through and through. Above all, Weber's position is attentive not to generalities but to singularities (Rabinow 2003: 35).

Secondly, Rabinow stresses that Weber understood the importance of perspective in seeking to grasp the "infinite multiplicity" of things which is possible to know:

One must, Weber underscores, have a point of view: 'In *which* sense and *which* situations this [significance] is the case is not revealed to us by any law; it is decided according to the *value-ideas* in the light of which we view 'culture' in each individual case.' (Rabinow 2003: 35).

Rabinow stresses that one should focus on empirical, tangible phenomena in order to ground the scope of one's inquiries. Equally (and not in contrast to the first point as some might suggest), one must grasp the changeable and socially embedded character of all phenomena. Who is speaking, and to whom, and under which particular constraints, matters to the importance of what is said. This thesis adopts a theoretical and methodological position in line with Rabinow's reading above of Weber. The intent is not to argue that particular phenomena, such as the results of randomized controlled trials, are untrue or unscientific, but that understandings of their truth or falsity are constituted through specific discursive, historical, social and personal practices.

A question still remains, however, of how best to access and analyze those specific social practices, particularly when practitioners themselves are often unaware of why they act in the ways which they do. To address this question, I have tended to turn away from Rabinow, and his arguable privileging of Foucauldian archaeological and genealogical investigations at the expense of an exploration of

individual subjectivities. My guide instead is Ian Hacking, and particularly the article “Between Michel Foucault and Erving Goffman: between discourse in the abstract and face-to-face interaction” (2004). In this work, Hacking describes the methodological influence and aims that have characterized his work, such as his concept of dynamic nominalism, where he asserts people strategically interact with categories of classification in ways that reciprocally affect those who are doing the classifying. He notes that two of his strongest influences are Foucault and Goffman, two scholars often misperceived – given Foucault’s inheritance from Weber, and Goffman’s from Durkheim – as standing in opposition. Hacking, in contrast, stresses their distinct yet complementary approaches:

In the past I have incorporated or adapted many of the kinds of analysis that Foucault developed (but not his remarkable style of writing). There is something missing in these approaches – an understanding of how the forms of discourse become part of the lives of ordinary people, or even how they become institutionalized and made part of the structure of institutions at work. Of course there is something absolutely missing in Goffman too: an understanding of how the institutions he described came into being, what their formative structures are. I am not concerned with completing Goffman, but rather with filling out Foucault...the two perspectives are complementary and both are necessary (Hacking 2004: 278).

Hacking’s insight lends support to those who have sought to contest the false dichotomization of Foucault versus Pierre Bourdieu, who was inspired by Goffman’s sociology (Bourdieu 1982). For, if Foucault has provided the tools necessarily for an investigation of the structures and modes of subjectification that categorizes the present, it is arguably Bourdieu – ensconced in the tradition of Durkheim and Goffman – who provides the tools necessary for what Hacking points out above as a question which Foucault may have paid insufficient attention to, how forms of discourse become a part of everyday life.

One writer who seeks to marry the insights of Foucault with those of Bourdieu is de Certeau (1988 (1984)). From Foucault, de Certeau notes, we gained

the crucial insight of how miniscule technologies comprise a microphysics of power which place individuals in regimes of discipline. And from writers such as Bourdieu and Goffman, furnishing as they do hypotheses which allow “the logic of unselfconscious thought to be taken seriously,” we are offered direction in identifying the tactics and practices of individuals already “caught in the nets of ‘discipline’” which Foucault illuminates (de Certeau 1984: xv). This insight provides direction helpful in the development of a methodology which takes from Foucault an awareness of the importance of institutional structures, and from Bourdieu an interest in the tactics of individuals who seek to subverting the structures Foucault identifies.

It is partly for this reason that I have sought to employ a combination of archival research, textual analysis and in-depth interviews. From Foucault, I have borrowed the tools of the archaeological analysis of discourses and texts. From Bourdieu and Goffman, I borrow the need to investigate social practices through observing and listening to the explanations people themselves give for their action – trying always to keep in mind that the things which are most relevant to individuals are often those which are the most difficult to articulate.

Study design and position of the researcher

In designing this study, a couple of personal factors have proved both advantageous and detrimental in various ways: one is my Canadian citizenship and the relatively short time (four years) I have spent living in the UK, the second is my background, both academic and professional, studying journalism and working briefly as a journalist in Canada. I elaborate on both factors below.

In approaching the archival components of this study, I approached the research much as a journalist would a story, by familiarizing myself with the various

factors – governmental, legislative, regulatory, economic – that had a bearing on the debates over whether SSRIs might lead to suicide in some users. This archival research consisted largely of the analysis of randomized controlled trials as presented in medical journals; the legislation, reports and transcripts of meetings from government bodies such as the UK's Department of Health and the Medicines and Healthcare Products Regulatory Agency (MHRA), the Department of Health, and the European Medicines Evaluation Agency (EMA); the trial protocols and promotional material of pharmaceutical companies which manufacture SSRIs; and the websites and press releases of UK patient and mental health organizations such as MIND and SANE. After spending six months familiarizing myself with this literature, I sent letters in early February 2005 requesting interviews with 15 psychiatrists and policymakers.

When it came to soliciting these formal interviews, I chose to focus – guided by Rabinow's study of the actors involved with the discovery of PCR – on a select, largely interconnected group of practitioners and working in the UK, most of them known to each other by name or in person, as allies, friends, and in some cases rivals. I derived their names from my archival research: From media reports; minutes from MHRA meetings; the websites of bodies such as the National Collaborating Centre on Mental Health (NCCMH), the Critical Psychiatry Network, and the Institute of Psychiatry, King's College. From such organizations, it was possible to generate a list of key figures, from psychiatrists to health activists, who had been vocal in some way during the recent debates over SSRIs: whether in asserting or denying the idea of a link between SSRIs and suicidal behaviour. Because some of the informants during early interviews referred often to problems with the quality of RCT data for SSRIs, and to problems within the evidence-based medicine movement itself, I later

expanded the scope of my inquiries to include questions concerning EBM, and spoke formally with two individuals who had no direct links to the SSRI controversy but were important figures in the EBM movement in the UK.

I received an overwhelmingly positive response to the 15 letters posted in February, 2005, with 12 out of the 15 replying almost immediately and offering to spare an hour of their time for a face-to-face interview at a location of their convenience. The high response rate is itself sociologically interesting. In some ways, the response could be explained by the fact that I had included the name of my supervisor, Nikolas Rose, on the letter, and he was acquainted with a number of the informants, in part through his research in the fields of psychiatry, psychology and the neurosciences. In other ways, the response rate revealed the timeliness of the topic – something which has been both beneficial and detrimental throughout the course of the research. Three months before I sent the letters, BBC's Panorama had aired the third programme in a series of three documentaries examining SSRIs, and the rather sensationalistic style of reporting on the programme seemed to have incensed both proponents and sceptics alike of the suggestion that SSRIs contributed to suicidality. Many of my informants expressed the hope to me that I would bring a measured academic sensitivity to an issue wildly distorted by ill-informed journalists (at this point I always felt obliged to admit I had worked as a journalist, to general dismay).

After sending initial query letters, most of the interviews took place between February 2005 and June 2005; some at London locations, such as the offices of the Royal College of Psychiatrists and the National Institute of Health and Clinical Excellence; others at academic institutions outside of London such as Bristol University. Although I requested interviews with a range of staff at the MHRA, I

only managed to secure one, with Professor Kent Woods, CEO of the agency. This interview took place in January, 2007, after approximately two years of requests to the MHRA's director of communications.

A question I faced has been whether or not to refer anonymously to my informants, many of whom are leading public figures in their respective fields. As it happens, however, only one of my informants requested I not use his name when it came to the writing of the thesis. As a rule, then, where a source has not made a specific request for anonymity, I quote him or her by name throughout. I realize this practice is contrary to general methodological styles within fields such as sociology. On this point my background in journalism has made it difficult to accept sociological convention. When a source is not in a position of vulnerability, and where the use of the data has been fully disclosed to an informant, I continue to find baffling, if not troubling, the sociological enthusiasm for pseudonyms or amalgamations of different informants into composite sources. One example is Richard Sennett and Cobb's otherwise stunning *The Hidden Injuries of Class*, where the authors note:

We have taken certain liberties beyond those necessary to protect anonymity: in various instances we have condensed remarks people made; when statements two people made on an issue were very similar, we have portrayed them as coming from one person. In a few instances we have put words in people's mouths, words they were struggling for, we felt, but couldn't find (Sennett and Cobb 1976: 42).

Such liberties, which threaten to distort the views and ideas of the sources themselves, seem contrary to the integrity of research that aims at empirical realism – as mine does. My goal therefore has been to clearly indicate to all informants that, if requested, I would guarantee their anonymity where possible, stressing that, given the small size of the research and policy community I was interviewing, the identities

of participants might be difficult to disguise. Each of the informants listed below gave their consent to being listed by name and institutional affiliation. In addition to those listed, I spoke with one individual, a consultant psychiatrist based in London, who requested anonymity. When referencing the interviews throughout the thesis, I have made occasional grammatical changes for clarity, keeping any edits as minimal as possible.

| | Name | Affiliation | Date of interview |
|----|--------------------------|---|-------------------|
| 1 | Tim Kendall | Co-director, National Collaborating Centre for Mental Health, deputy director of the Royal College of Psychiatrists' College Research Unit, and medical director and consultant psychiatrist in the Sheffield Care (NHS) Trust. | February 2005 |
| 2 | Richard Brook | Then Director, MIND, and former member of the MHRA's Committee on Safety of Medicines' Expert Working Group on SSRIs | February 2005 |
| 3 | John Geddes | Professor of Psychiatry, Oxford University; head of Centre for Evidence-Based Mental Health | February 2005 |
| 4 | Stuart Donovan | Practicing epidemiologist | February 2005 |
| 5 | David Healy ¹ | Professor of Psychiatry, Cardiff University | March 2005 |
| 6 | Susan Bailey | Former Chair of the Royal College of Psychiatrist's Faculty of Child and Adolescent Psychiatry | March 2005 |
| 7 | David Nutt | Head of Community-Based Medicine Professor of Psychopharmacology, University of Bristol | March 2005 |
| 8 | Charles Medawar | Health care activist and author, Social Audit | April 2005 |
| 9 | Timothy Fox | Former practicing GP | May 2005 |
| 10 | Michael Shooter | Then president, UK Royal College of Psychiatrists | May 2005 |

¹ The interview with Healy did not record properly, and I therefore have no transcript. But I have stayed in touch with him fairly regularly and, particularly, as he read and commented on a version of Chapter Four, I feel comfortable that I have accurately reflected his views and position on the SSRI debates.

| | | | |
|----|------------------|--|---|
| | | | |
| 11 | David Gunnell | Professor of epidemiology, Bristol University, and former member of the MHRA's Committee on Safety of Medicines' Expert Working Group on SSRIs | June 2005 |
| 12 | Joanna Moncrieff | Lecturer in psychiatry, University College London; and co-founder, Critical Psychiatry Network | Sept 2005 |
| 13 | Iain Chalmers | Editor, James Lind Library, Oxford | March 2006 (joint interview with Glasziou) |
| 14 | Paul Glasziou | Head, Centre for Evidence-Based Medicine, Oxford University | March 2006 |
| 15 | Kent Woods | Chief Executive Officer, MHRA | January 2007 |

I have stayed in fairly regular contact with a number of these sources – in particular Tim Kendall, David Healy and Iain Chalmers – allowing for informal follow-up discussions at various points over the last two years. In addition, a second formal interview took place with Kendall in December 2006 and was subsequently published in the journal *BioSocieties* (Kendall and McGoeys 2007).

Ethically, my main concern has been to ensure, particularly given that I have chosen to disclose the identity of informants, that each informant was aware of my intention to publish material from the thesis. During interviews, I found individuals were extremely forthcoming – something I attributed in part to the generational, gender and national disparities between the majority of my subjects and myself, as well as to the fact that, as I found while studying journalism, sources are often more forthcoming when speaking to students, whom they perceive as more innocuous than professional journalists or academics. In order to ensure I had not unfairly represented myself, I sought to make it clear that I was both a PhD student as well as

a published journalist with some access to media outlets, albeit with contacts mostly restricted to Canada. I also offered to show any interested informant a copy of the transcript – amenable to their minor edits.

This last measure, advised during methodology courses at the London School of Economics, is something that astonished me at first given my background in journalism, where the practice of inviting a source to view or amend a story before it is published is widely condemned. Particularly when speaking with public individuals with considerable authority, whose decisions have implications for individuals more vulnerable than themselves, such as Kent Woods, the ethical course of action in journalism is to consider the public import of disseminating a sensitive statement to be of *greater* significance than the potentially negative repercussions to the individual. Exceptions are of course abundant – if a source stresses something is “off the record,” one’s duty lies in maintaining the right to confidentiality.

With time, however, I have been persuaded by the sociological emphasis on sharing one’s research with informants. Particularly in areas where I quote from the scientific literature on SSRIs, and, as a non-scientist, have wanted to ensure the scientific rigour of my analysis, I have on occasion asked an informant to read over areas where they are referenced. I have sought in particular to be very cautious in ensuring I had full consent from the informants named in Chapter Four, where I argue that a strategic use of ignorance was employed by regulators in order to absolve themselves of liability in not disclosing the adverse effects of SSRIs when they first learned of them.

This finding is based in part on interview data with Richard Brook, who was threatened with legal prosecution in a letter from Kent Woods for seeking to publicly reveal information about the inefficacy of SSRIs at certain dosing levels. Brook

discovered the information about dosing levels while serving as an expert advisor to the MHRA's 2003-2004 SSRI expert working group. I initially completed this thesis chapter in the summer of 2006. In the fall of 2006, I submitted a revised version of the chapter to the journal *Economy and Society*, which published the article in May 2007. While the piece was under consideration, I sent a copy to Brook to ensure the validity of his quoted comments. He confirmed in an email that he was in agreement with his quotes, as well as my interpretation of events.

It was not until after the article was accepted by *Economy and Society* that I was granted an interview with Kent Woods. During this one-hour interview, I told both Woods and the media relations officer present throughout I had a forthcoming article that was fairly critical of the MHRA. I have since sent a copy of the article, as well as a transcript of my interview with Woods, to the MHRA. Given that no one at the MHRA voiced objections to the transcribed interview, I feel comfortable quoting freely from it in this thesis and in published material, despite the fact that Woods made a number of comments which I found surprising, and which portray the MHRA in a slightly contentious light, such as the following:

the further I go in this job, the more I see that actually the social aspects of what we do are very important. In the sense – just as a final comment: when I came into this job, the relationship, the role of the regulator was seen very much as a dialogue with industry. You bring us a product, we'll tell you whether you can market it, end of story. Actually, it's a far more complicated relationship than that. We have an external constituency – the public and patients. And most of our job is actually putting out good quality information on the risks and benefits of medicines, on which patients and prescribers can make wise, informed decisions. That has never been seen, up until a few years ago, as the role of the regulator (LM interview with Kent Woods, January 2007).

In some ways Woods' comment is unsurprising; given the MHRA's relationship and funding reliance on industry, it is understandable staff would see their job as one of ensuring relations with industry were intact. In other ways, the comment is slightly startling, not so much for its content, but for the fact that Woods

himself is explicit that the needs of industry have historically taken precedence over the needs of patients.

I think this excerpt provides a good opening to state my own political position leading to this research, which I entered with a number of biases. I was active in political “anti-globalization” activism in Canada, and many of the news articles I sold were critical of institutions such as the International Monetary Fund, World Bank and the G8. I started the PhD out of an interest in critically observing some of the practices of pharmaceutical companies. For the most part, my concerns with industry, particularly with the tendency to withhold negative clinical trial results from regulators and the public, have only deepened as a result of my research. On the other hand, I have become frustrated with sociological analyses which harangue the pharmaceutical industry or the inadequacies of regulators without seeking to explore the *motives* of a company or a regulator for acting in certain ways.

A final point on methodology: I chose at the outset of my research to focus my formal interviews on “expert” actors involved in the controversy, rather than to approach the debates from the perspective of patients groups and family members of those who have either died or attempted suicide while on SSRIs. Despite this, I was occasionally put in touch with such family members, and my informal discussions with these individuals have contributed profoundly to the study. Similarly, I have sought regular conversations with individuals who work in finance – as financial analysts, brokers and so on – and are knowledgeable, if only peripherally, about the economic implications of the recent series of drug controversies affecting the pharmaceutical industry. Here I have followed the methodological example of Nigel Thrift in *Knowing Capitalism*:

The ‘method’ that I have used in this book consists of three elements: reading across a wide range of sources (from formal academic accounts through the

press (broadly defined) to all manner of informal documents), observant participation (for example, talking on a fairly continuous basis to business people), and, in particular, looking for what I call chains of clues, where one piece of information seems to lead inexorably on to the next in a way which suggests that a trail is being followed but which is really an artefact of looking in the right place at the right time (Thrift 2005: 17).

In Chapter Seven, for example, where I compare the case of SSRIs to the case of Merck's Vioxx, it was an informal discussion with a family member – a retired investment manager – that led in part to my analysis of the usefulness of uncertainty to industry groups. Offhand, the family member mentioned to me he had invested in Merck's stock immediately following the withdrawal of Vioxx. I asked him later how the stock was doing, and he replied, via email:

I purchased at approximately \$27 US and it is currently trading around \$45 (I am pleased). They were successful in having each lawsuit tried separately (which I think makes sense as each case can be different), rather than as one large class action lawsuit. As a result it will take years and years to try each case, and for each legitimate case that they may lose there are those cases that are bogus or semi-bogus that they will win. It will still obviously cost them billions over the years in legal fees and successful claims, but perhaps less than if they rolled the dice on one class-action lawsuit and probably less than the market's worst fear. In the meantime Merck is able to profitably carry on business (LM personal email, April 2007).²

This family member's offhand comment led me to query a common observation voiced by both regulators and sociologists, which is that it is not in a company's economic interest to withhold clinical trial data from either the public or from regulators. In the case of Merck's Vioxx, few today dispute, as I describe in more detail in chapter seven, that the company purposefully distorted clinical trial data (Horton 2004; Topol 2004; Jasanoff 2006). What remains unclear is whether the strategy of manipulating data proved financially detrimental or, as this email

² Eight months after this email, in November 2007, Merck announced it had reached a \$4.85 Billion settlement in 27,000 suits covering about 47,000 plaintiffs (Krauskopf 2007). The amount was, as my source predicted, far less than the "market's worst fear." On the news of the settlement, Merck's stock jumped 2.1% to \$57.04 per share. I explore the case of Vioxx in greater detail in Chapter Seven.

suggests, beneficial for some of Merck's investors – particularly for those attracted to the company during its post-Vioxx slump. In sum, offhand comments drawn from informal discussions have been important in shaping some of the theoretical suggestions in the thesis.

Review of literatures

The thesis contributes to the sociological literature in three main areas: 1) The social construction, methodology and use of randomized controlled trials; 2) social implications of evidence-based medicine, which I link to analyses of the social and political consequences and implications of claims to objectivity within medicine; and 3) the usefulness and value of ignorance and uncertainty to regulatory and industry bodies.

The material I have drawn on traverses a wide range of disciplinary fields and schools of thought (Weber 1922 (1995); Weber 1978); the history and philosophy of science (in particular Daston and Galison 1992; Daston 1994; Porter 1995; Proctor 1996); anthropology (in particular Rabinow 1996; Petryna 2002; Rabinow 2003), and to political theory, political economy and studies of risk and regulation (particularly Power 1994; Luhmann 1998; Rose 1999; Rose 1999; Rose 2001; Power 2003; Hutter and Power 2005).

I have been inspired in this attempt at disciplinary flexibility by Ian Hacking's response to his own question in *Historical Ontology*: "What role should social studies have in historical ontology? This is precisely the sort of methodological question that I find useless. I help myself to whatever I can, from everywhere" (Hacking 2002: 17).

The social and political construction of randomized controlled trials

Although a number of sociologists have analysed the political structure of drugs regulation in Britain and the EU (for example Abraham 1995; Busfield 1996; Abraham and Sheppard 1999; Corrigan 2002; Corrigan 2002; Abraham and Smith 2003; Busfield 2006), less attention has been paid to the rise, construction and implications of randomized controlled trials (RCTs), something that is surprising given that RCTs are the dominant technology for determining the efficacy and safety of most medical treatments. RCTs are defined as:

An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body) (Cochrane 2007)³

RCTs that are “double-blind” (neither the scientist nor the patient knows which participant have received the active treatment and which the control, or no intervention) are considered the ‘gold standard’ of medical research. In order to license a new pharmaceutical product in the UK, US and Europe, companies must show a certain number of successful RCTs to regulators such as the Food and Drug Administration (FDA) in the States, or its equivalent in Britain, the MHRA.

Problems surrounding the design of RCTs have long been noted by scholars outside the field of sociology (Kaptchuk 1998; Quitkin 1999; Miller 2000; Healy 2001; Moncrieff 2004). Only recently, however, have sociologists and anthropologists begun to examine the history and construction of RCTs in any depth.

³ Generally, UK policymakers and clinicians refer to RCTs as randomized *controlled* trials, while in the US, they are often called randomized *clinical* trials. The difference is simply semantic.

In the past few years, sociologists have begun to explore things such as difficulties in translating the data from RCTs to general clinical use, and gender inequities in deciding which patients should participate in trials (Adams 2002; Corrigan 2002; Corrigan 2002; Dehue 2002). The historian Harry Marks has published the most comprehensive study of the history of RCTs in the US (1997). In anthropology Adriana Petryna (Petryna 2005) and Vinh-Kim Nguyen (Nguyen 2005) have examined the politics of the outsourcing of RCTs to developing regions. In philosophy, Nancy Cartwright at the London School of Economics is currently leading a project investigating RCTs, causality and dissent in science (Cartwright 2007) and bioethicist Richard Ashcroft (Ashcroft 1997; 2004) has published analyses on the ethical implications of RCTs (see Ashcroft 2007; Wahlberg and McGoey 2007).

This thesis expands on these investigations by exploring the social factors that are central to the design of RCTs, and by drawing attention to a number of factors that can hinder an RCT from producing valid evidence about the safety profile of a given drug. Drawing on medical literature on the safety and efficacy of SSRI antidepressants (Ferguson 1990; Geddes and Cipriani 2004; Whittington, Kendall et al. 2004; Martinez, Rietbrock et al. 2005; Whittington, Kendall et al. 2005; Cipriani, Barbui et al. February 19, 2005), I examine a number of factors, such as biases in the patient inclusion criteria for RCTs, which can affect the outcome of clinical trial results. One of my aims is to stress that the problems with the clinical trials for SSRI antidepressants are not specific to this class of drug, but are associated with the design, publication and implementation of RCTs in general.

Further to this, a key aim of the thesis is to develop a sociological framework for theorizing the implications of RCTs. As noted earlier, I do so by applying

Latour's concept of inscription devices to the realm of RCTs, arguing that, during debates over drugs, individual clinical trials often have a rhetorical function that has little to do with the scientific reliability of the trial.

Secondly, I suggest that because RCTs are employed by clinicians to serve as evidence in a system of medicine that increasingly validates scientific evidence over emotion or personal judgement, RCTs have a tacit moral function. Any attempts to question or to critique the reliability of RCTs therefore inadvertently casts doubt on the credibility of individual prescribers. As a result, practitioners have a vested interest in maintaining the appearance of the scientific independence and validity of RCTs – strategically ignoring the ways that commercial factors have influenced their construction. Drawing on work by Michael Power, I argue that while individual RCTs may be scrutinized, medical practitioners have a strategic interest in maintaining the perception of the methodology of RCTs as free of partisan influences.

Thirdly, I argue that RCTs close the space for dissent and disagreement among clinicians and policymakers by serving as scientific, and therefore seemingly incontestable, tools for determining the safety of treatment. Rose has suggested that there is a mutually constitutive relationship between numbers and modern forms of governance: as well as helping to constitute modern forms of governance (e.g. by serving as diagnostic instruments in defining support through electoral polling, or in determining areas of governance through censuses), numbers serve to “redraw the boundaries between politics and objectivity by purporting to act as automatic technical mechanisms for making judgements, prioritizing problems and allocating scarce resources” (Rose 1999: 198). This insight is supported by Barry's suggestion that political arenas are increasingly restricted to experts and advisors capable of

arbitrating on technical and instrumental matters. Building on this work, I suggest RCTs have a depoliticizing function by purporting to render evidence about drugs scientifically valid and therefore beyond the scope of contestation.

Finally, as clinical trials are the dominant technology for determining a medicine's safety within evidence-based medicine, I suggest that problems surrounding the design, publication and interpretation of RCTs illuminates a number of weaknesses within evidence-based medicine itself.

Evidence-based medicine and the “moral authority of objectivity”

There has been a number of analyses of evidence-based medicine since its emergence over four decades ago (for example Armstrong 2002; Flynn 2002; White and Willis 2002; Goodman 2003; Timmermans and Berg 2003; Mykhalovskiy and Weir 2004; Timmermans and Mauck 2005; Daly, Willis et al. 2006; Will 2007). With the exception of a number of nuanced analyses from scholars such as Eric Myhalovskiy, Lorna Weir, Marc Berg, Stefan Timmermans and Catherine Will, many of the sociological studies of EBM have tended to be unhelpfully vitriolic, such as Holmes and colleagues comparison of EBM to a form of “microfascism” (Holmes, Murray et al. 2006), or, in the case of many proponents of EBM, uncritically normative, with “EBM-ers” suggesting that the tools and methodologies of EBM are indispensable for conducting any manner of social or medical investigation.

A recent article from Jeanne Daly and colleagues provides an example of the latter tendency. Entitled “A hierarchy of evidence for assessing qualitative health research” (2006), the piece proposes a taxonomy of qualitative research studies, with single case studies at the lowest band of significance, and generalizable studies at the

apex of the hierarchy. The proposal's explicit devaluing of case-based research is the type of suggestion resented by qualitative researchers whose methods, from ethnographic research to discourse analysis, have often sought to elucidate the social phenomena lost through a privileging of quantitative studies.

Recently, a colleague Ayo Wahlberg and I acted as guest editors of "An elusive evidence-base: The construction and governance of randomized controlled trials," a special volume of the journal *BioSocieties* (Wahlberg and McGoey 2007). The issue brought together work from scholars (such as Catherine Will, Nancy Cartwright, Andrew Lakoff, David Armstrong, Adriana Petryna and John Abraham) who sought to avoid the polemical tone that has characterized previous sociological observations of EBM to date.

One of the things we sought to achieve in the special issue was a more sensitive and nuanced characterization of EBM advocates themselves. Often, those who espouse the values of EBM are painted with a broad brush, and internal fissures among epidemiologists, clinicians and policymakers, as well as regional differences in the implementation of things such as clinical practice guidelines, have not been adequately scrutinized. In this thesis, I address this gap by drawing on interviews with individuals who have played a leading role in the development of EBM in the UK, such as Iain Chalmers, one of the founders of the UK's Cochrane Collaboration, Paul Glasziou, head of the Centre for Evidence-based Medicine in Oxford University, and Tim Kendall, co-director of the UK's National Collaborating Centre for Mental Health, which is responsible for formulating most of the clinical practice guidelines in the area of mental health for the UK's National Health Service.

This thesis builds on previous analyses of evidence-based medicine through a focus on two main areas. Firstly, I explore problems surrounding publication bias

and the disclosure of clinical trial data to government regulators and the public.

Currently, there is no legal onus on pharmaceutical companies to publicly disclose data where a treatment is shown to be inefficacious or harmful. As a result, national clinical guidelines which are authoritative for the NHS are routinely based on no more than half of all available clinical trial data possessed by industry and regulators (Kendall and McGoey 2007).

Recently, partly as a result of the public controversies over drugs such as the SSRIs and Vioxx, pharmaceutical companies have established voluntary clinical trials registries where they post details of clinical trials (Rennie 2004). As a result, however, of the voluntary nature of these databases, there is little enforcement in place to ensure companies post trials (Kendall and McGoey 2007: 137). Related to this, the illusion of compliance seems to have deflected attention from industry's ongoing efforts to evade disclosure (Chalmers 2006).

Secondly, I suggest that EBM has grown in tandem with the rise of the "moral authority of objectivity" (Haraway 1991; Daston and Galison 1992; Daston 1994; Rose 1999; Daston and Sibum 2003), something I define as a cultural ethos within medicine that limits the ability of clinicians to voice dissent unless their objections are restricted to the universe of quantifiable phenomena. The problem is not that the *desire* to voice critiques has diminished. If anything, as the very willingness of individuals to meet with me indicates, the recent suggestions of corporate misconduct at a number of different pharmaceutical companies has politicized many practitioners. But that, as ever more political and moral authority is vested in randomized controlled trial data by regulators, policymakers and clinicians, it has become increasingly difficult for individual criticisms to have salience unless one's objections are clothed in the language of numbers.

In 2006, the philosopher Lorraine Daston gave the Tanner Lectures on Human Values at Harvard University, on the topic of “moral authority of nature.” Later, she and Fernando Vidal edited a book of the same title, bringing together a series of articles to explore the relationship between nature and moral standards and norms. In their foreword, they stressed the intention to move beyond controversies over social constructivism and realism, to shift “the focus of inquiry from the existence and (il)legitimacy of nature’s authority to its jurisdictions and workings” (Daston and Vidal 2004: 2). My use of the term moral authority of objectivity is drawn from Daston and Vidal, and with it I borrow their goal to shift discussions from the real versus constructed nature of objectivity to a study of the implications of the authority of objectivity in practice.

This approach echoes Porter’s argument in *Trust in Numbers* (1995), where he argues that the social and political legitimacy of numbers – their social and moral aspects – has yet to be adequately appreciated by either scientists or those who study them. Since the 1970s, he notes, debates surrounding objectivity have instead been polarized over questions of realism, and what constitutes as objective truth. Porter suggests this is both a mistake, and a diversion from practical concerns, such as the personal and political implications of claims to objectivity in any given field. Porter stresses that his working definition of objectivity seeks to imply nothing of questions of realism and truth. Instead, his focus is on the resources that objectivity commands, the strategies of trust and authority which it comprises, and the suppression of judgement which it fosters. I adopt a similar perspective and working use of objectivity.

Although work from Andrew Abbott (1988) and Eliot Friedson (Friedson and Lorber 1972; 1975; 1986) on professionalism, from Thomas Gieryn (1999) on the

cultural boundaries of science and medicine, and from Paul Rabinow (Rabinow 1996; Rabinow and Dan-Cohen 2005) on ethical work among scientists, has investigated organizational practices and professional “boundary work” among medical practitioners and scientists, this work does not account for the difficulties clinicians face in seeking to translate private misgivings with the corporate structure of medicine into public concerns. The heuristic of the moral authority of objectivity is helpful in exploring this question. Further, I examine the relationship between the moral authority of objectivity and the value of ignorance and uncertainty to government regulators. What is the relationship between uncertainty and the validation of objectivity, disinterest, neutrality and impartiality? How have those in positions of authority profited from the rhetoric surrounding objectivity? Answers lie in the third broad area of literature relevant to the thesis: studies of ignorance, uncertainty, regulation and risk.

The value of ignorance and the performative nature of uncertainty

In Chapter Four, I suggest that MHRA regulators employed a strategic use of ignorance in order to absolve them of the failure to act swiftly when evidence first arose of the adverse affects of SSRIs. Theoretically, I explore the regulatory usefulness of ignorance by drawing on studies from sociology, anthropology and philosophy, such as Nietzsche’s suggestion that “will to non-knowledge, to the uncertain, to the untrue” is a refinement of the will to knowledge (Nietzsche 1990 (1973): 55), and Michael Taussig’s suggestion that often the most important knowledge is “knowing what not to know” (Taussig 1999: 9). My argument here draws on, and contributes to, to work in the area of bureaucracy and regulation, particularly to literature on the factors that can hinder a regulator from enforcing

compliance to regulatory or legal rules (DiMaggio and Powell 1983; Hawkins 1989; Weick 1998; Hutter 2001; Hawkins 2002; Lentzos 2003; du Gay 2005; Hutter and Power 2005; Reed 2005; Vaughan 2005).

In Chapter Seven I return to a discussion of the value of ignorance and uncertainty, drawing on Barry's (2006) work on the interrelation of secrecy and transparency, as well as literature from science studies and the sociology of knowledge and ignorance (Smithson 1989; Smithson 1993; Proctor 1996; Galison 2004; Michael 2004; Wynne and Irwin 2004; Balmer 2006; Proctor 2006; Townley 2006), economic sociology and political economy (Arnoldi 2004; Thrift 2005), and risk and regulation (Daemmrich and Krucken 2000; Ericson and Doyle 2004; Power 2004; Hutter and Power 2005; Power 2005; Power 2007).

My focus throughout the thesis on the value of ignorance and uncertainty illuminates a number of limitations with Beck's work on risk, such as his suggestion that we have entered a period of "second-order, unnatural, human-made, manufactured uncertainties and hazards beyond boundaries...so the hidden central issue is *how to feign control over the uncontrollable*" (Beck 2002).

As criticisms of Beck's thesis of a world risk society are widespread, I will outline just two weaknesses here. The first is his suggestion that there is something profoundly novel about the manufacture of risks and uncertainties. In my view, the manufacture of risks has always existed; the key difference is that scholars such as Power and Proctor are shedding light on why certain risks are selected over others, as well as pointing out that the management of risk often serves as a resource to those who are called upon to manage the risks which they themselves have fostered (Douglas and Wildavsky 1980; O'Malley 2004; Power 2004; Proctor 2006; Power 2007).

Secondly, I am sceptical of Beck's distinction between "bads" and "goods," the idea that some risks are productive and others detrimental; some uncertainties insurable, others unmanageable. My views are closer to Richard Ericson and Aaron Doyle, who point out, in an article on the response of the global insurance industry to 9/11, that:

while in some times and places insurers are indeed what Beck terms "technological pessimists" and "economic pessimists," they also take risks for profit. In other words, they speculate and gamble. They thrive on uncertainty, to the point where in some respects their calculation of risk is not so much a matter of frequency and severity, but rather threat and opportunity (Ericson and Doyle 2004: 137).

Work by scholars such as Ericson, Power, Proctor and Thrift on the value of risk and uncertainty helps to support the theoretical argument advanced in the last chapter of the thesis: the idea that uncertainty is performative and productive, often working to consolidate the authority of those who have advanced a position to begin with. Uncertainty is also exonerating, as in the case of the SSRI controversy, where regulators, whether consciously or not, drew on the scientific uncertainty surrounding the RCTs for SSRIs in order to absolve past regulatory errors.

The last point on uncertainty indicates a final contribution of this thesis: its illumination of the value and usefulness of both uncertainty and ignorance to scientists, policymakers and regulators. This analysis contributes to the small literature that has explored the implications of ignorance and "social unknowing" (Turner 1978 (1998); Thrift 1985) in political and regulatory structures and in science and medicine (for example Smithson 1989; Smithson 1993; Michael 2004;

Balmer 2006), developing a number of taxonomies that seek to distinguish between uncertainty and ignorance.⁴

The most useful is Michael Smithson's taxonomy of ignorance and uncertainty, where he points out one of the main distinctions at root in forms of ignorance: knowing that we don't know versus *not* knowing that we don't know (Smithson 1989; Smithson 1993). Smithson expands on this through a discussion of the difference between "being ignorant" (which is equivalent to not knowing something), and the "act of ignoring," which he calls a "declaration of irrelevance." Drawing on work from Mary Douglas and Barry Turner, Smithson notes that people tend to ignore things as a result of numerous pressures, such as the need to adhere to social taboos, or to the institutional constraints that make it difficult to process information, something Turner illuminates in his account of why information is often purposefully discounted by individuals who have no place for the information "within prevailing modes of understanding" (Smithson 1993: 140). I return to this insight in Chapter Four, where I discuss the usefulness of ignorance to government regulators in absolving them of past regulatory failures.

The brief summary above on work on ignorance is useful for illuminating a key difficulty facing my research, which is the need to choose an adequate working distinction between uncertainty and ignorance. It is obvious that there are many differences – semantic, emotive, practical – between the two words. In the *Oxford English Dictionary*, uncertainty is defined as "the quality of being uncertain in

⁴ In a personal email, Smithson noted he has been disappointed by the lack of attention to the study of ignorance over the past twenty years. Despite isolated studies of "social unknowing," to use a phrase of Thrift's from 1985, there has been surprisingly little attention to the social and political uses of ignorance. The trend appears to be changing. Robert Proctor, for example, is editing a volume on agnotology, Proctor's term for the cultural reproduction of ignorance, which is scheduled for publication by Stanford University Press in 2008. Bringing together work by Smithson and others, the volume may prove to be the first general reader in social studies of ignorance.

respect of duration, continuance, occurrence, etc. liability to chance or accident,” while ignorance is defined as “the fact or condition of being ignorant; want of knowledge” (Oxford 2007). These definitions adhere to what Smithson notes has been the traditional distinction between ignorance and uncertainty: ignorance is treated as either the absence or the distortion of “true” knowledge, while uncertainty is viewed as incompleteness in information or knowledge. He argues this distinction is inadequate, because it suggests that to talk of ignorance “we must have established criteria for absolute knowledge and epistemology,” something constructivist critics of the objective nature of knowledge generally reject (Smithson 1993: 136).

A second limitation of these established definitions is that they imply that when one talks of “strategic ignorance,” as I do in Chapter Four, a more apt term might be “strategic uncertainty,” for it seems only logical that the word “strategy” cancels the possibility of total ignorance. When one speaks of “strategy,” it seems apparent a situation has moved from the “unknown” to the “uncertain,” therefore rendering strategic uncertainty a more appropriate phrase.

I argue against this. Strategic ignorance and strategic uncertainty are separate phenomena; they hold value for different reasons. The most importance distinction is that by employing the former, one has recourse to the exculpatory power of complete non-knowledge: an appeal to ignorance provides justification for non-action or for misguided action. The use of strategic uncertainty is less exonerating. Acting erroneously on the basis of partial knowledge is typically less forgivable than acting erroneously (or choosing not to act) on the basis of no knowledge at all.

On the other hand, strategic uncertainty has a number of uses which strategic ignorance does not. Among these, as I elaborate in Chapter Seven, is the usefulness of uncertainty in lobbying for more scientific or policy resources, or in casting doubt

on the completeness of a rival's research. Uncertainty is also invaluable to what Proctor's calls "filibuster research" or the commissioning of ever more scientific studies to cast doubt on earlier ones (Proctor 2006). In such instances, the admission of complete ignorance seems less likely to elicit resources than an admission of partial knowledge. Throughout the thesis, I elaborate on these and other distinctions between strategic ignorance and uncertainty.

As a final note on methodology and literature: I indicated earlier that I have combined formal discussions with informal discussions with family members, colleagues and acquaintances interested in the political and economic implications of debates over SSRIs. Just as I draw on both informal and formal interviews, I draw on "informal," non-academic literature throughout, from popular books on psychiatry such as Lauren Slater's *Prozac Diary* (Slater 1998), to memoirs, both online and published, of those who have lost children while on SSRIs, such as Linda Hurcombe's *Losing a Child* (Hurcombe 2004).

Particularly influential have been a number of recent publications that have illuminated that economic and political value of uncertainty, such as Naomi Klein's *The Shock Doctrine: The Rise of Disaster Capitalism* (2007), which explores a paradoxically undervalued platitude: the fact that economic instability is often lucrative. Also exploring the value and the productivity of market volatility, if from a separate ideological perspective, has been work by traders turned self-styled philosophers such as Nassim Nicholas Taleb, whose *Fooled by Randomness* notes:

In the market, there is a category of traders who have *inverse* rare events, for whom volatility is often a bearer of good news. These traders lose money frequently, but in small amounts, and make money rarely, but in large amounts. I call them crisis hunters. I am happy to be one of them (Taleb 2004: 112).

This thesis explores the emergence of a particular crisis during the peak of evidence-based medicine – the controversy over SSRIs and the question of whether they contribute to suicidal reactions in some users. In seeking to understand what at first seems indefensible – a company’s decision to distort clinical trial data, or a regulator’s need to turn its gaze from such behaviour – the statement above helps to remind of the obvious: the rationality and usefulness of an act is always contingent on perspective. One person’s crisis is another’s gain, and for many the refusal to know is often the most valuable form of knowledge.

Chapter 3: Drugs regulation and the politics of objectivity in medicine

Introduction

In this chapter, I describe the emergence of evidence-based medicine, a model of medicine which has had a profound impact on the regulation of medicine and the provision of health services in both the UK and internationally since its inception over four decades ago. I argue that an oversight within previous literature on EBM medicine, from both clinicians and sociologists, has been their lack of attention to how problems of regulation have rendered it difficult to fulfil the practical aims of EBM. I assert that the main regulatory obstacle contributing to weaknesses within EBM is that, despite the emphasis placed on the importance of RCT evidence in guiding treatment decisions, UK policymakers do not have legal access to all available RCT evidence on a given treatment. Inequalities in access to clinical trial data have been at the heart of the controversy over the safety of SSRIs, where, despite the emergence of early anecdotal evidence suggestive of adverse side-effects, practitioners have at times been vilified by their peers for voicing their concerns unless they could draw on RCT evidence to legitimate their objections.

This chapter begins with a description of the emergence of evidence-based medicine in Britain. I then provide a description of the size of the pharmaceutical industry in Britain. This description is crucial to the third and final section of the chapter: a summary of the British drugs regulatory system.

The rise of EBM in Britain and internationally

In the early 1970s, a British epidemiologist Archie Cochrane published a short book which, to the surprise of many observers – policymakers, physicians and Cochrane himself – was to have a revolutionary influence on the practice of medicine in Britain and North America. The volume, *Effectiveness and Efficiency: Random Reflections on Health Services*, made a few short and to-the-point remarks. First, Cochrane argued that medical decisions should be made with better scientific knowledge of which treatments were effective and which were not. Second, he argued that health care needed be more economically efficient. Third, Cochrane stressed the need for greater equality in medical provision across socio-economic groups. As a young medical student, Cochrane had once marched alone through the streets of London carrying a homemade placard that read “All effective treatments must be free.” Cochrane had wanted to bring equality, efficiency and cost-effectiveness to health care. The first of his goals – the desire to increase equity in health care – receives only the occasional mention by advocates of his work today. But the latter two, medical efficiency and medical cost-effectiveness, are spoken of with near religious fervour by those determined to realize some of the ideas sketched in his slim 1972 volume.

Thanks in part to those advocates, Cochrane’s work has played a large role in the development of evidence-based medicine (Cochrane 1972; Cochrane 1987; Rogers 2004), a term first coined by a group of clinical epidemiologists working out of McMaster University in Canada in the early 1990s (Mykhalovskiy and Weir 2004), who later defined EBM as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett 1996).

One of the founding principles of EBM is that there should be systems in place to compare available data on a treatment, for example through the development of meta-analyses, or syntheses of individual research studies (in Chapter Five I provide a history of the development of RCTs themselves). The development of research syntheses emerged from the realization among researchers in a number of fields, from health research to the social sciences, that there often existed more than one well-conducted experiment in a given area which had yielded different results. The methodologies of “research synthesis” and “meta-analyses” grew in response to the challenge of finding rigorous, scientific ways to combine, integrate and assess the findings of multiple studies in a given area (Berg 1995; Marks 1997; Chalmers, Hedges et al. 2002; Marks 2003). Though debates still abound over the reliability and scientific exactitude of meta-analyses, their use in health policy is growing ubiquitous.

There have been periodic attempts over the past two centuries to synthesize the results of available medical studies. It was not until the 20th-century, however, that “the science of research synthesis as we know it began to emerge” (Chalmers, Hedges et al. 2002: 14). One early effort was Joseph Goldberger’s 1907 analysis of statistics on typhoid fever in the District of Columbia. Goldberger’s methodology followed a number of distinct steps which, Chalmers notes, are now considered standard in efforts today to compare and statistically assess the results of studies in a given area. Firstly, Goldberger identified 44 comparable studies; secondly, he delineated specific criteria for selecting which studies to include in a statistical analysis; thirdly, he extracted data from the selected studies, and lastly, he implemented a statistical analysis of the pooled, selected data.

Chalmers notes that, contrary to the view that the tactics of research synthesis originated in health research and epidemiological circles, it was actually social scientists working in the United States, some having to deal with 345 different studies of the effects of interpersonal expectations on behaviour, or 833 tests of the effectiveness of psychotherapy, who began to recognize the need for systematic reviews in order to assess the reliability of individual studies. People working in health research, Chalmers writes, were relative latecomers to research synthesis, most remaining unaware of the problems of the “collective ignorance” of separate, contrasting studies until Cochrane observed that “it is surely a great criticism of our profession that we have not organized a critical summary, by speciality or subspecialty, adapted periodically, of all relevant randomized controlled trials” (Cochrane, quoted in Chalmers, Hedges et al. 2002: 20).

This goal of Cochrane’s – to develop critical summaries of all available data on a treatment – has been the guiding aim of centres such as the Cochrane Library, founded in Oxford, England in the early 1990s. This first library has led to dozens more across the world, broadly administered within the auspices of two parent organizations: The Cochrane Collaboration, and the US-based Campbell Collaboration. These organizations have led in part to one of the most controversial developments in medicine and health care in recent years – the growth of bodies, such as the National Institute for Health and Clinical Excellence,⁵ which commission research and produce evidence-based treatment guidelines that physicians are directed to use in their clinical research. Since the early 1990s, EBM has fostered a host of new journals, and is now routinely taught as the dominant approach to

⁵ NICE was founded in 1999, almost a decade later than a number of US organizations founded to provide clinical guidelines across the United States. For a history of the development of US bodies equivalent in scope and goal to NICE, see Heimer et al 2005. Throughout this thesis, I limit my discussion of problems surrounding clinical practice guidelines to the UK context.

research and practice in medical schools throughout North America and Europe. The reach of EBM has extended far beyond medicine, influencing things such as social work, government policies on economic aid and social care, and international development programmes (Mykhalovskiy and Weir 2004).

Among proponents, EBM is often viewed as a democratizing element in health care. It is regarded as improving access to clinical research data, and increasing the ability of patients to challenge decisions made at the personal discretion of physicians. As two advocates wrote in a recent article: “[EBM] challenges the paternalistic and authoritarian nature of much medical practice...Culturally, its anti-authoritarian spirit is important in increasing the participation of different stakeholders and opportunity for a multi-disciplinary approach to health care problems” (Liberati and Vineis 2004). There is much rhetorical strength in the arguments of those who suggest EBM has had an democratizing effect, for to oppose EBM suggests one is in favour of maintaining a rigid hierarchy between doctors and patients. A difficulty for critics is that EBM is often framed, as Mykhalovskiy and Weir note, as an entirely win-win situation: “Who can argue with better evidence? Who would take issue with more effective and better quality evidence?” (2004: 1067).

Despite this, criticisms are increasingly audible. Some suggest, for example, that efforts to standardize behaviour erode a physician’s ability to respond to the changing needs of individual patients. Also, that physicians are induced to justify their decisions through rationales of cost containment rather than on patient care (Armstrong 2002; Hammersley 2005). This line of thought often situates the rise of EBM within the general shift in the last thirty years to models of managed care, and the institutionalization of ‘health technology assessment’ exercises and ‘clinical

governance' schemes, suggesting that EBM should be seen as part of wider state efforts among neo-liberal governments to restrict the economic and political autonomy of clinicians (Flynn 2002).

Some see this as a positive development. As two proponents suggest, EBM might be viewed "as a solution to the problem of drug company influence over medicine: limitations on professional and patient autonomy are justifiable, because both groups make irrational developments based on commercial marketing" (Saarni & Gylling 2004: 174).

Another charge is that EBM forces a move away from treating the patient as an individual with a specific life history. EBM is viewed as a universalizing technology which perceives the individual as simply an aggregate of a research population. Observers also suggest that EBM discredits the value of anecdotal evidence gathered from patients themselves, dismissing their personal descriptions of illness as less reliable than the statistical evidence derived from populations. This last point alludes to questions concerning the epistemological roots of EBM.

The title of a recent article, "Positivism resurgent: the epistemological foundations of evidence-based medicine," encompasses the basic lines of the philosophical debates over the rise of evidence-based medicine. To quote the article above, the model can be seen "as an appeal to positivistic canons of scientificity which have been systematically challenged by both the philosophy and the sociology of medicine" (White and Willis 2002). In line with this, critics suggest that EBM has led to the development of a hierarchy of evidence, where the more 'objective' evidence derived from RCTs is viewed as superior to the knowledge derived from the personal experiences of individual patients. The notion rests, as one observer

notes, on the questionable belief “that it is possible to rank methods of inquiry by their susceptibility to bias” (Ashcroft 2004: 131).

Some observers have taken debates over the epistemological roots of evidence-based medicine to questionable lengths, writing diatribes against the movement that have managed to alienate EBM proponents and critics alike. One example, mentioned earlier, is the recent article for Holmes and colleagues which suggested EBM was “outrageously normative and dangerously normative with regards to scientific knowledge,” and could be considered a “good example of microfascism at play in the contemporary scientific arena” (Holmes, Murray et al. 2006: 180). The authors’ contention that EBM represents a pernicious effort to expel diversity from debates over health care, fostering a situation where individuals must resort “to resistance strategies in front of such hegemonic discourses within which there is little freedom for expressing unconventional truths” (2006: 182), is somewhat undermined by the outlet where their views are published: *The International Journal of Evidence-Based Healthcare*. Unsubstantiated criticisms from writers such as Holmes have managed to polarize participants affected by the shift to EBM, making it harder for measured critics to find an audience for more nuanced observations.

In some ways, questions about the nature of evidence within RCTs and EBM might be viewed as simply a recent materialization of the centuries-old arguments over questions of objectivity vs. subjectivity; ‘pure sciences’ vs. ‘social sciences;’ biological reductionism vs. socially and culturally sensitive analyses. The question then becomes one of how to both investigate and expand on the sociological observations of evidence-based medicine without simply repeating the debates over whether scientific knowledge should be viewed as a social construction like other

systems of knowledge (for example Barnes 1974; Latour and Woolgar 1979, 1986; Latour 1999; Hacking 2002).

One way to move beyond question of realism and constructivism is to argue that, as it is difficult to validate the extreme end of either a strict constructivist or a strict realist perspective, one should look more closely at the political and social conditions through which certain truths and systems of scientific knowledge are produced. As Rose notes, “it is not very enlightening to be told repeatedly that something claimed as ‘objective’ is in fact ‘socially constructed’... so the interesting questions concern the ways in which they are constructed. Where do objects emerge? Which are the authorities who are able to pronounce upon them? Through what concepts and explanatory regimes are they investigated?” (Rose 1999 (1989): x).

Drawing on work by Rose and others, this thesis explores the moral authority of objectivity within evidence-based medicine. What interests are served by the validation of certain types of evidences, such as the evidence from RCTs, over others? Whose interests are displaced? In order to answer such questions, I examine EBM in relation to larger political and social structures in Britain, exploring how regulatory factors, such as the relationship between the Medicines and Healthcare Products Regulator Agency (MHRA) and the pharmaceutical industry have affected the development and delivery of the aims and goals of EBM.

The relationship between the pharmaceutical industry and drugs regulation in Britain

As noted earlier, a main finding of this thesis is that, across a number of areas of medicine, UK policymakers who are responsible for formulating national guidelines on the safety and effectiveness of medical treatments are frustrated by the fact that they have inadequate access to the clinical trial data necessary for forming

solid guidance. Some proponents of EBM suggest that gathering clinical trial data into widely accessible databases such as those monitored by the Cochrane Collaboration will make it easier for clinicians to access the latest evidence on best treatments, resulting in more robust standards of health care. Findings from my analysis of the SSRI controversy suggest, however, that a number of structural factors weaken the quality of the clinical trial evidence that is stored in databases such as the Cochrane.

One such factor is the relationship between the pharmaceutical industry and the MHRA – the body responsible for all pharmaceutical licensing and post-market safety surveillance. Because of Britain's Medicines Act 1968, described in more detail below, the MHRA is hindered from publicly disseminating all of the clinical trial data that is relevant to a drug's safety profile. Thus, the clinical trial data that results in databases such as the Cochrane have been filtered through numerous processes of institutional censorship. Institutional structures dilute the quality of evidence that policymakers, practitioners and patients rely on in the prescription and consumption of a drug. A key limitation within the paradigm of EBM has been the failure among many proponents to recognize these numerous institutional limits on the circulation of medical evidence.

I argue that this weakness stems from a problem with the way many advocates conceptualize the evidence from RCTs. Among advocates, much faith is placed in the scientific rigor of RCT data, for the very justifiable reason that RCTs are the sole medical experiments which systematically control for bias through the use of random allocation of treatments to active and control arms. RCTs are not the sole form of evidence employed by regulators and policymakers in order to determine the risk / benefit profile of a particular treatment, or to develop clinical practice guidelines.

But they are the form of evidence placed at the apex of hierarchies of quantitative and qualitative methodologies in licensing drugs and forming treatment guidelines; systematically drawn on as the most scientifically robust tool for determining a treatment's worth. Among most clinicians, practitioners and regulators, RCTs are viewed as the "gold standard" in medical research (see Timmermans and Berg 2003; Kendall and McGoey 2007).

Partly as a result of this perception, many advocates argue that a benefit of EBM has been the growth of databases such as the Cochrane which foster access to RCTs studies, and make it possible for patients, clinicians and policymakers alike to access data on a drug or other treatment, reaching his or her own conclusions on its merits. But in practice, do clinicians or patients have the resources to search for relevant RCT data? Or, more crucially, to question the quality of that data? To examine how it has been affected by a range of political and regulatory filtering processes? In the remainder of this chapter, I address these questions by focusing on the size and composition of the pharmaceutical industry in Britain, and on the relationship between the pharmaceutical industry with the MHRA.

Scale and scope of the pharmaceutical industry in Britain

I think it's absolutely clear that the pharmaceutical industry has not been open with all its results. Negative as well as positive. I think that some of the trials themselves that they have run have been biased to some extent. I think that some of the publications, some of the articles written around results have been flawed. And I think the regulatory bodies – the MHRA in this country, the FDA in the States, and the European equivalents – it feels as if they have been hoodwinked (LM interview with Michael Shooter, May 2005).

In interviews with practitioners, in archives detailing past controversies over the safety of psychotropic drugs, and on the websites of patient organizations, one finds sentiments similar to that voiced by Michael Shooter, former president of the Royal College of Psychiatrists, in the excerpt above. Many observers attribute the

emergence of the SSRI controversy to the size, political weight and practices of the pharmaceutical industry, in Britain and internationally. That industry, observers claim, has suppressed evidence of the medical dangers of SSRIs. It has buried the results of clinical trials, bought the opinion of leading medical experts and bullied the drugs regulator in Britain into approving unsafe medications. Such accusations are not the lone ramblings of extremist activists. They are the opinion of an increasing number of individuals, from patients to practitioners, in Britain.

Such opinions were the focus of a recent House of Commons inquiry into the influence of the pharmaceutical industry on health policy in Britain (HOCa April 2005). They were at the centre of a recent front-page article in the *New York Times*, which noted that only nine per cent of Americans felt US drug companies were completely honest about their practices. Thirty-four per cent of Americans, meanwhile, trusted the honesty of banks, and thirty-nine the integrity of US supermarkets (Berenson 2005).

Sociologists have long taken an interest in the size, structure and influence of the pharmaceutical industry. Abraham (for example 1995; Abraham and Sheppard 1999; Abraham and Smith 2003) has focused on the politics of the drugs industry within Britain, while a number of social scientists have explored the dynamics of the international pharmaceutical industry (Braithwaite 1984; Chetley 1990; Nichter and Vuckovic 1994; Farmer 1999; Lakoff 2004; Mossialos, Mrazek et al. 2004; Rose 2006). These analyses are joined by a range of work outside of the social sciences, from journalists, policy analysts, and medical practitioners, who are increasingly starting to scrutinize the practices and influence of industry (for example Medawar 1992; Relman and Angell 1992; Walker 1993; Bury 1996; Healy 1997; Healy 2002; Angell 2004; Healy 2004; Medawar and Hardon 2004).

Partly as a result of suggestions of dubious industry tactics, the UK Parliament's Health Select Committee chose to convene an inquiry, from September 2004 to February 2005, into the pharmaceutical industry's influence on health policy in Britain. The inquiry was the first large-scale government investigation of the influence of the drugs industry since the Select Committee on Patent Medicine reported to Parliament on August 4, 1914 (HOCa 2005). It was large in scope, and touched on a number of general aspects concerning the manufacture, production and regulation of pharmaceuticals that are central to an understanding of the specific trajectory of the controversy over SSRIs. Indeed, as a number of practitioners I spoke with noted, the vociferous debates surrounding SSRIs, instrumental as they were in raising public attention to the influence of the pharmaceutical industry, helped to spur the establishment of the Parliamentary inquiry in the first place. A number of the expert witnesses called before the Health Select Committee had been participants in the debates over the safety of SSRIs. Reciprocally, the final report from the Health Select Committee touched specifically on the controversy over SSRIs as emblematic of what the report describes as inefficiencies in the regulation of drugs in Britain.

The Health Committee is one of a number of select committees of the House of Commons, groups which are composed of politicians and MPs from all parties. Select Committees may choose to examine any area of public significance. They then invite oral and written evidence from parties relevant to the area under examination, and produce reports to which the government is obligated to respond to (Smith September, 2005). The Health Select Committee was, at the time of the inquiry into the drugs industry, composed of eleven Members of Parliament: Six Labour, two Conservative, two Liberal Democrat and one Independent. These members held nine oral hearings over the six-month duration of the inquiry, receiving evidence from, as

the final report describes, “Ministers and officials from the Department of Health and the Department of Trade and Industry; health professionals and academics; the pharmaceutical industry; journalists, PR companies; patient organizations; medical charities...NICE and the MHRA” (HOCa: 9). They also received over 100 written submissions of evidence. To help guide the scope of the inquiry, the Select Committee appointed a team of five specialist advisors. These advisors included John Abraham, Professor of Sociology at Sussex University, and Charles Medawar, Executive Director of Social Audit, an independent research institute that has been instrumental in raising concerns about the safety of SSRIs. Alongside the publication of the Committee’s final report in April, 2005, the Health Select Committee published full transcripts of the evidence from its nine oral hearings, as well as copies of the written memoranda submitted to the inquiry.

For a number of reasons, the Parliamentary inquiry has been a helpful resource in the researching of this thesis. Firstly, the final report provides a comprehensive overview of the political and economic structure and size of the pharmaceutical industry in Britain. Secondly, an analysis of the transcripts from the oral hearings reveals a number of implicit findings that are not explicitly evident in the Committee’s final report. The transcripts indicate, for example, that very few of the Members of Parliament on the Health Committee had any understanding of the funding structure of drugs regulation in Britain prior to the Parliamentary inquiry.

The excerpt below illustrates this lack of prior knowledge. The excerpt is taken from questions directed by the Committee to Lord Norman Warner, Parliamentary Under-Secretary of State for Health. They concern the operations of the Medicines and Healthcare Products Regulatory Agency, the main government agency responsible for drugs regulation in Britain.

Q919 Dr Taylor: We are told that the MHRA is one of only two European Agencies for whom the operation of medicines regulatory system is funded entirely by fees from services to industry and many people have implied to us that it must be incredibly difficult actually to protect the public from unsafe medicines when you are being paid by the very people who are producing those compounds. How do you rate the independence? How do you ensure it when they are being paid by the very people they are trying to regulate?

Lord Warner: ...there is no evidence that this form of funding has in any way skewed the decision making of the [MHRA]. It has also separated operationally within the agency pharmaco-vigilance from the licensing; it has separated that work under the chief executive, so you do not have the same people doing the licensing as are doing the pharmaco-vigilance in post-licensing....

Q921 Dr. Taylor: When the regulatory system came in – and I am old enough to remember the problems with thalidomide and it came in after the thalidomide episode – was it funded by industry right from the start? Has it always been funded by industry? What happened initially? (HOCb 2005: Ev 375)

I quote Taylor's confusion and questions in order to stress a key point. Many times throughout the House of Commons' inquiry, MPs returned to questions surrounding the ambiguous and secretive nature of the MHRA, trying with difficulty to obtain clarity from the MHRA staff called as oral witnesses during the inquiry. Given the fact that Members of Parliament on a government committee focused on the structure of health care in Britain had little understanding of the nature, management and funding mechanisms of the MHRA – and found it hard to elicit responses from the MHRA staff serving as oral witnesses – it is little surprise that “everyday” practitioners, for want of a better label, are becoming increasingly frustrated with what they view as the lack of transparency and accountability surrounding pharmaceutical regulation in Britain.

Size and structure of the UK pharmaceutical industry

The pharmaceutical industry in the United Kingdom directly employs approximately 83,000 individuals and, after tourism and finance, represents the country's third most profitable economic sector (HOCa 2005). It is, as the Health

Select Committee reports, the fifth largest pharmaceutical sector in the world, representing seven% of world pharmaceutical sales, after the US, Japan, Germany and France. The industry is represented in Britain by the Association of the British Pharmaceutical Industry (ABPI), which notes, in a memorandum submitted to the Health Select Committee, that ABPI member companies (of which there are over 80) manufacture and supply more than 80% of the medicines prescribed through the NHS. The ABPI notes that the pharmaceutical industry is the largest contributor to research and development in Britain, spending a total of £3.3 billion annually, or £10 million every day. Such innovation has resulted in a quarter of the world's 100 top-selling medicines originating in research and development carried out in the UK (HOCb 2005: Ev 308).

As the Health Select Committee notes, medicines cost the NHS in England £7 billion every year, 80% of which is spent on branded products. The purchase of medicines accounts for 12% of the NHS budget. 650 million prescription items were dispensed in England in 2003, amounting to an average of 13.1 prescription items per head. The Health Select Committee flagged this level of prescription as excessive, noting that current rates of prescription represent “a 40% increase over the previous decade. The cost of prescriptions dispensed in England has risen remorselessly with year-on-year increases well above inflation. In 1993 the cost was £3.1 billion. In 2003 it was £7.5 billion, an increase of 9.7 % or 6.4% in real terms on 2002” (HOCa 2005: 7).

The Committee stressed a number of concerns with the increased level of drugs consumption in Britain. In particular, in the Committee's final report, and during the oral hearings held throughout their inquiry, Committee members returned often to the problem of medicalisation, defined in the report as an “unhealthy reliance on, and

over-use of medicines – the view that there is a pill for every ill” (HOCa 2005: 8). A key concern of such over-use, the Committee noted, is that it leads to increased exposure to the risk of drug-induced illness and harm. Such adverse drug reactions account for at least 3% to 5% of all annual hospital admissions, and cost the NHS at least £500 million per year.

When called as witnesses before the Health Select Committee inquiry, staff and executives at pharmaceutical companies rejected the charge that increasing drugs sales were contributing to an unwarranted medicalisation of society. The ABPI, in its written submission to the Health Select Committee, quoted the NHS Chief Executive’s 2003 report which stated that increases in the prescribing of medicines were contributing to improvements in health care, in particular to an improvement in survival rates for cancer and coronary heart disease. The ABPI added that: “The pharmaceutical industry is proud of what it does. Our goal – to bring to patients life-enhancing medicines – it is not only necessary but noble, and there is no reason why the industry should not use all legitimate means to advance it” (HOCb 2005: Ev 307).

One means of advancing industry interests is through the fostering of academic-private partnerships, and through funding post-graduate medical education. In 2003, UK pharmaceutical companies sponsored over 1,100 collaborations in 80 UK institutions. As the ABPI notes, a recent report sponsored by the HM Treasury found that the industry “is exemplar not just in research intensity, but also in its approach to collaborative research with universities” (HOCb 2005: Ev 310).

Critics argue it is precisely this level of academic sponsorship that is fostering an inappropriate amount of industry influence on the post-graduate education and the prescribing patterns of physicians. A recent article in the *British Medical Journal*

notes that over half of all post-graduate education in medicine is funded by the pharmaceutical industry. The industry has a total marketing budget of £1.6 billion for such things as public relations, the sponsoring of education, promoting pharmaceuticals to physicians, and the sponsoring of conference presentations by “key opinion leaders” who often receive up to £5,000 for giving an hour-long talk. The Department of Health, conversely, spends just £4.8 million annually on the publishing of independent material on drugs, or just 0.3% of the amount spent by industry on marketing (Ferner 2005).

There is a growing number of medical practitioners who are starting to lobby against the pervasiveness of industry sponsorship. An organization called *No Free Lunch*, which originated in the United States and now has a subsidiary arm in Britain, is geared at raising awareness of industry influence, and which is active in lobbying for more regulatory curbs on pharmaceutical marketing. In my interviews with practitioners, however, many suggested that the majority of physicians remained unconcerned – at least unable or unwilling to articulate concerns – with industry involvement. There is the sense, some practitioners described, that regular visits from pharmaceutical sales representatives are seen as an enjoyable diversion from the routines of daily practice, and that small tokens or gifts can add a welcome touch to staff meetings or seminars. As one of my respondents, a consultant psychiatrist living in London, noted of the general reception of industry involvement:.

I organized a debate at the local hospital to try and talk about the influence of drug companies, and we used the theme of free lunches and the *No Free Lunch* campaign which there is in America. Where you can download stickers and stuff and put them in your hospital. We had an interesting debate and at the end of the day we had a vote and the majority of people wanted to continue to get a free lunch provided...People said it's one of the attractions of coming to the meetings. They get a sandwich (LM interview with senior psychiatric consultant, March 2005).

Throughout their inquiry into the pharmaceutical industry, members of the Health Select Committee returned often to the question of the pharmaceutical industry's sponsorship of medical events and conferences. The following excerpt provides an example. The exchange is between a member of the Health Select Committee and David Healy, an outspoken critic of the safety of SSRIs and a witness to the Select Committee inquiry on Oct. 14, 2004.

Professor Healy: what you find these days is people like me are brought to the Caribbean. We come out of the meeting halls with our arms stuffed full of free gifts, free rulers, free pens, free mugs, that have the name of the drug on them. We have had our massage done, portrait painted –

Q157 Mr Amess: You have had your massage done?

Professor Healy: People have had their massage done, their portrait painted...

Q158 Mr Amess: Before moving on to my next question. You have got an awful lot off your chest; you want to have a get together with the Free Lunch chap! Did you enjoy your time in the Caribbean?

Professor Healy: Well, yes, I am in a position to speak to all these things, and the issue was raised earlier, having worked very closely with industry, having been a person who has actually spoken for the industry; so I know just what the practices are....the drug reps when they come round to see me will have the free pen and the free mug...

Mr Amess: This is all very interesting. Members of Parliament could never be influenced in such a way! (HOCb 2005: Ev 94).

Members from the Health Select Committee were sufficiently concerned with pharmaceutical sponsorship to flag the problem of marketing levels among the 48 conclusions and recommendations made in the Committee's final report. These recommendations covered a range of areas. Key among them was the call for an independent review of the MHRA, and the suggestion that the responsibility for representing the interests of the pharmaceutical company should move from its current remit within the Department of Health, to the remit of the Department of Trade and Industry, in order to allow the Department of Health to concentrate

solely on the promotion of health and the regulation of drugs. The Committee noted the following rationale for this recommendation:

Government has a dilemma: it has to balance the need to promote the competitiveness of this industry with the need to address health concerns and to promote the effectiveness of the NHS. The Department of Health has constantly to balance trade imperatives and health priorities. This is a hard task. Sometimes, it means serving two masters at the same time (HOC I: 9).

The recommendation to shift the responsibility of promoting industry from the Department of Health (DOH) to the Department of Trade and Industry (DTI) in order to mitigate conflicts of interest illustrates what many viewed as a fundamental weakness of the Health Select Committee's inquiry in general. Critics argue that the pharmaceutical industry has such deep ties to Parliament itself – and particularly with the New Labour government – that any attempts to switch sponsorship of industry from the DOH to the DTI does nothing to curb industry favouritism. Some have suggested that because of the extent of liaison and collaboration between pharmaceutical industry representatives and members of the UK government, the Health Select Committee's inquiry into the influence of the drugs industry on health policy in Britain might have been better framed as an independent inquiry into the drug industry's influence in Parliament (Walker 2004).

In 1999, for example, a significant meeting took place between Prime Minister Tony Blair and the Chief Executive Officers of AstraZeneca, Glaxo Wellcome and Smithkline Beecham. At the meeting, the CEOs argued that a restrictive regulatory environment was impinging on the UK industry's ability to compete internationally (HOCa 2005: 14). The meeting led to the establishment of the Pharmaceutical Industry's Competitive Task Force (PICTF), a group co-chaired by the Parliamentary Under-Secretary of State for Health Lord Hunt of Kings Heath and Tom McKillop, CEO of AstraZeneca. Under the PICTF, the government identified a number of

factors that could help encourage competitiveness, such as the development of a more rapid regulatory process for medicines in comparison to other countries.

Upon the publication of the PICTF's final report in 1999, a number of subsequent government-industry collaborations were established, at least three of which continue to meet on a regular basis. In an online article, journalist Martin Walker offers an example of such a collaboration. In November, 2001, as a result of PICTF recommendations, a body called the Associate Parliamentary Group for Health (APGH) was established. The group consists of representatives from the House of Commons and House of Lords, including David Amess, Conservative MP for Southend West, who also serves on the House of Commons Health Select Committee, and was quoted earlier, questioning David Healy on the influence of pharmaceutical donations on physicians. Alongside representatives from the Commons and Lords, APGH consists of associate members from companies such as Bayer, Novartis, Pfizer and Wyeth. Each associate member provides £5,000 per year toward the running of the APGH, which holds a host of seminars, breakfast meetings and receptions in buildings adjacent to the House of Commons, where ministers and MPs are able to meet and liaise with executives from the pharmaceutical industry (Walker 2005).

As Walker notes, the establishment of all-party Parliamentary groups by commercial lobbies is something that has occurred on a fairly regular basis throughout the Labour government. This level of industry-government partnership is not surprising in itself. What is of interest, though, is the expression of faith, in the Health Select Committee report, that switching explicit sponsorship of the pharmaceutical industry from the Department of Health to the Department of Trade and Industry would mitigate conflicts of interest. Such a move, I suggest, would have

no such impact. Firstly, it would have no influence on the informal industry relationships fostered through regular meetings between members of groups such as the APGH. Secondly, as I describe in more depth below, the transfer would have no direct impact on the actual structure of drugs regulation in Britain.

History of Drugs Regulation in Britain

Since 1989, the licensing and post-surveillance of drugs has been the responsibility of the MHRA, an executive, semi-autonomous agency of the Department of Health. The operations of the MHRA are wholly funded through fees charged to the pharmaceutical industry for the service of licensing pharmaceuticals. Throughout the transcripts from the Health Select Committee's oral hearings one finds a sense of bafflement, voiced by both MPs holding the hearings, and by witnesses giving oral evidence, about the particularities of the MHRA's structure and organization. In order to provide an overview of the regulatory context that helped foster the emergence of the controversy over the safety of SSRI antidepressants, the remainder of this chapter provides a description of the history and structure of the drugs regulatory system in Britain.

Members of the Health Select Committee might be forgiven their sense of confusion about this system, given numerous internal changes since formal establishment thirty-five years ago. Beyond the confusion created by a host of internal reconfigurations, some observers suggest a second reason for the general lack of understanding, among politicians, practitioners and patients, of the current medicines regulator in Britain. They argue that the regulator works in an atmosphere of secrecy which makes it difficult for any interested party – from patient groups to health care policymakers – to obtain adequate information about the safety of drugs.

The following section describes the establishment of the current regulatory system, situating its emergence in the wake of the Thalidomide scandal of the 1960s. Thalidomide, sold in the UK by the Distillers Company, was available on the British market for just three years, from 1958 to 1961. Its short period of availability on the market, though, proved catalytic. The Thalidomide catastrophe, which resulted in an estimated 10,000 birth defects worldwide, ended for many British citizens “the age of innocence, and led to the opening of parts of the health-care system to a degree of public scrutiny and control never known before” (Medawar 1992: 74). The first step in formal legislation was the introduction of the Medicines Act, passed in 1968 and implemented in 1972. During that same period, the Sainsbury report was published, which identified a number of problems in the regulation of the pharmaceutical industry in Britain. As a result of this report, two bodies were set up, firstly the Medicines Commission, and then the Committee on Safety of Medicines (CSM), to advise the government on the safety of pharmaceuticals. Though the CSM remains relevant today as the key advisory group to the current Medicines and Healthcare Products Regulatory Agency (MHRA), the Medicines Commission itself has waned in authority and relevance to current regulatory structures. The government has recently announced that both the Medicines Commission and the Committee on Safety of Medicines are now to be replaced by a new, unified body, called the Committee on Human Medicines (Collier 2005). This body, like the CSM before it, will continue to act as an advisory group to the key agency in Britain’s drugs regulatory system: The MHRA.

The history of the MHRA takes some nuance to describe concisely. Most recently, in 2003, the regulator was changed from the Medicines Control Agency [MCA] to its current organization as the MHRA, as a result of a merger between the

medicines control and medical devices agencies. The MCA, which preceded the MHRA, was established in 1989 when the UK government, under Margaret Thatcher, moved to make the drugs regulator semi-autonomous from the Department of Health (DOH). Unlike its predecessor body (a body which operated as a division within DOH), the new MCA relied, and continues to rely, on fees paid by pharmaceutical companies in exchange for drug licensing services. A number of other EU countries generally adopted this model of industry funding to some extent in the 1990s (Abraham and Smith 2003; Mossialos, Mrazek et al. 2004). In comparison, the Food and Drug Administration (FDA), the US equivalent of the MHRA, has a funding structure that is divided between public and private financing. Currently, half of the funding for the FDA's Centre for Drug Evaluation and Research, which oversees drug reviews and drug safety, comes from industry fees (Harris 2004).

Though the funding of Britain's drugs regulator is not unusual in comparison to other British industries (many regulators were similarly made into privatised, executive agencies of various government bodies during the Thatcher era), there remains a level of public apprehension about such a funding arrangement. In short, individuals suggest that the reliance on industry fees in order to run their operations makes it difficult for MHRA employees to act independently when it comes to the licensing of drugs. Those in favour of the current system, on the other hand, argue that the funding structure is to the financial advantage of British citizens. They note that, as it is pharmaceutical companies which profit financially from the sales of drugs, those companies, and not taxpayers, should be covering the licensing costs of pharmaceutical drugs. The system is unlikely to change in the near future in ways that would mitigate the concerns of those critical of industry funding. If anything, the

move by EU member states to adopt systems similar to the UK's indicates the increasing acceptance, across the European Union, of industry-funded drugs regulators.

Following the move to make the regulator an executive agency of the DOH, the second significant shift in the history of Britain's drugs regulatory system was the introduction of new European regulations in the mid-1990s. Though a level of European integration on pharmaceutical policies has existed since the mid-1960s, that integration increased significantly in 1995 when the European Medicines Evaluation Agency (EMA) was established. Since the establishment of this agency, a pharmaceutical company's ability to market a new drug in countries across Europe, previously a wholly national procedure, has increasingly come under the remit of the European Commission (Mossialos, Mrazek et al. 2004: 6). Elias Mossialos, a leading health economist, notes that there are a number of concerns with the structure and oversight of the EMA. For example, the EMA is regulated by the EC Directorate-General of Enterprise. Such oversight, he points out, suggests that the priorities of the EMA might be more aligned with the interests of industry than with ensuring the safety of new drugs. Were the EMA to be regulated by Directorate-General for Health and Consumer Protection, Mossialos suggests, then "its objectives might be more aligned with the interest of patients" (Mossialos, Mrazek et al. 2004: 7).

Sociologists such as Abraham (Abraham 1995; Abraham and Sheppard 1999; Abraham and Smith 2003), have also raised a number of concerns with the structure of the EMA, and its influence on national regulators such as the MHRA. Under EMA regulations, if a drug company wishes to market a product in more than one EU member state, they first apply to a national regulator, which then seeks approval from other member states where the company wishes to market the drug. The bulk of

company licensing fees goes to the member state where the pharmaceutical company has first applied for a licence. The result, Abraham notes, has been the creation of an internal EU market where national regulatory agencies compete for the fastest approval times, in order to gain the most possible income from pharmaceutical companies (Abraham 2001; Abraham and Smith 2003). Some observers suggest that as a result, new drugs are being rushed through licensing processes – to the detriment of patient safety. Abraham notes that, because of such concerns, the issue of whether national regulators are sufficiently transparent and publicly accountable has become one of paramount importance. Unfortunately, as Abraham has pointed out – in a sentiment voiced repeatedly in my interviews with practitioners – the British regulator is not (Abraham 2001).

Transparency and accountability at the MHRA

The MHRA has a budget of £65 million and employs 750 staff (HOCa: 30). Alongside the facilitation of initial licence approval, the MHRA has responsibility for providing post-market surveillance: it must monitor the appearance of adverse effects after a licence has been granted. It employs a number of measures for such surveillance, including the administration of what is known as the “Yellow Card Scheme.” The scheme allows physicians to voluntarily file reports of adverse drugs reactions experienced by their patients. The scheme has been viewed negatively by a number of critics, who note that its voluntarily nature has resulted in the significant underreporting of adverse effects (Medawar 1992; Medawar and Hardon 2004).

As the Health Select Committee’s final report notes, MHRA staff themselves acknowledge the problem of underreporting. In the case of Merck’s Vioxx, for example, the anti-inflammatory removed from the British market in September,

2004, the Yellow Card system failed to provide any significant signal of the fact that, as was finally established in 2004, Vioxx was responsible for heart attacks in some users. In a second area of concern, observers have criticised the Yellow Card system for providing no means for patients themselves to report adverse drug reactions to the regulator. The MHRA has recently addressed this criticism, launching two pilot programmes which allow patients to directly report suspected adverse effects via the MHRA's website.

In interviews with practitioners, I found that the question of the appropriateness of the MHRA's funding structure was only about third in importance on their list of concerns with the regulator. Of deeper concern was the question of the severity of commercial confidence laws in Britain which critics argue favour the pharmaceutical industry at the expense of consumer safety. The UK government's 1911 Official Secrets Act and Section 118 of the 1968 Medicines Act, for example, prevent MHRA regulators from publicly divulging any commercial information related to the licensing applications for medicines. If staff members, or any member of an MHRA advisory committee, do divulge such information, they face serving jail terms of up to two years for breaching commercial confidence laws (MHRA 2006). As a result, regulatory staff and expert advisors on MHRA working groups are barred from publicly discussing any aspect of a pharmaceutical company's license application (including evidence of adverse drug effects) discovered during the application process. It was the stringency of the stipulations laid out in Section 118 of the Medicines Act that, for example, prevented the UK regulator from even explaining to physicians its reasons for removing the product licence for Halcion, a benzodiazepine believed to cause dependence in some users (Medawar and Hardon 2004). Similarly, observers close to the public debates over SSRIs have suggested it

has been the severity of Section 118 that has prevented MHRA staff from publicly sharing evidence of adverse side effects in SSRIs when staff members first learned of such effects.

As noted earlier, a principle belief in EBM is that gathering information from RCTs into public databases such as the Cochrane Library will help to facilitate the ability of practitioners to access evidence and information, resulting in higher standards of health care. Paradoxically, however, because of the privacy laws detailed above, the MHRA is hindered from publicly disseminating all of the clinical trial data that is relevant to a drug's safety profile. It is, in fact, a criminal offence for them to divulge all of the clinical trial data relevant to a company's application for a new drug licence. Thus, the clinical trial data that is publicly accessible has been affected by processes that dilute the quality of the evidence practitioners and patients rely on in the prescription and consumption of a drug, and policymakers at bodies such as NICE rely on in formulating clinical practice guidelines. For the majority of psychiatric drugs, for example, "less than half, and maybe only a third on average, of clinical trials are being published" (Kendall, quoted in Kendall and McGoey 2007). A key weakness within the paradigm of EBM, I suggest, has been the failure to acknowledge the numerous institutional limits on the circulation of medical evidence.

A second general concern voiced often by those who are critical of the MHRA's structure is the question of the professional independence of MHRA staff, executive directors and expert advisors. Alongside the question of whether the MHRA's general funding structure impinges on the independence of the regulator, some argue that the level of individual industry involvement among many MHRA staff and advisors suggests a problematic conflict of interest. An excerpt, for

example, from the recent Health Select Committee hearings indicates a concern for inappropriate levels of what Members of Parliament characterize as “cross-dressing” among authorities at the MHRA. The following excerpt is taken from an exchange between David Hinchliffe, Chairman of the Health Select Committee, and Lord Norman Warner, at the time serving as Britain’s Parliamentary Under-Secretary of State for Health. MPs noted a concern for Warner’s involvement with the pharmaceutical industry as co-chair of the Healthcare Industry Task Force (HITF), a joint industry-government initiative launched in 2003.

Q998 Chairman: Cross-dressing in politics is apparently quite fashionable, but you seem to be in an impossible cross-dressing position in the role you have. What I am interested in are your thoughts. What would be the impact if the commercial aspects, the competitiveness task force aspects of your role, were actually within DTI and the regulatory remained within Health? Can you see any advantages or can you see disadvantages? Obviously this is an issue which, as you appreciate, has been thrown around throughout the inquiry.

Lord Warner: Once you separate those two functions it would be far more difficult to get the right balance. You set up the scope for conflict departmentally within government if you go down that path and I would still cite Europe in that particular case. Where the going gets rough in public expenditure terms and you have a slightly embattled health minister trying to cope with a burgeoning budget against the wishes of some of his colleagues...where you get that, there is always the danger that the short-term considerations, in terms of balancing the health budget, will over-predominate[.]

Q999 Chairman: What you are saying is that this cross-dressing I referred to is not an impossible task from your point of view.

Lord Warner: I do not want to come across as a fervent cross-dresser and I never quite see myself in those terms, but if that is the label the Committee wish to apply to me, I am comfortable in that position (HOCb 2005: Ev 386).

Throughout the Health Select Committee inquiry, MPs returned to the questions raised with Lord Warner: to the problem of whether the MHRA, because of conflicts of interest among individual staff members, and because of its funding structure, is overly indebted to the interests of the UK pharmaceutical industry. MPs concluded in the Health Select Committee’s final report that this level of

indebtedness has resulted in a climate of regulatory ineffectiveness. One area where MPs felt the regulator had been particularly inefficient was in the detection of adverse effects in SSRIs. As they note in the Select Committee's final report:

Regulatory inertia was clearly illustrated through the findings of the UK's first ever public investigation into a drug safety problem: the December 2004 report of the CSM's Expert Working Group (EWG) into the safety of SSRI antidepressants....some 10, 15 years after the licensing the major SSRIs, and in spite of several earlier reviews of the same drug problems, the MHRA had received no convincing evidence of [drug efficacy in mild depression; or the incidence of SSRI withdrawal rates] (HOCa 2005: 19).

The Health Select Committee's final report is surprisingly outspoken in its criticisms of both the pharmaceutical industry and of the MHRA. As I noted earlier, the report made a total of 48 recommendations. These ranged from the call for the establishment of an independently regulated clinical trial registry, to the inclusion of lay patients on MHRA advisory committees.

Recommendations from Parliamentary groups such as the Health Select Committee are not binding on the government. Thus far, aside from a few intimations of the possibility that more lay representatives will be included on MHRA committees, the UK government has not implemented any of the Health Select Committee's suggestions. Most observers are not of the opinion that it will do so in future. A recent article in *PLoS Medicine* (a publication of the US Public Library of Science), for example, notes that the Health Select Committee report "will probably be less remembered for its recommendations – most of which will probably be ignored – than for having brought the important debate over the excessive influence of the pharmaceutical industry to a wider public" (Smith 2005: 822). Most of the practitioners I spoke with did not seem consoled by the suggestion that the Health Select Committee's report had served as a helpful exercise in public relations. They remained deeply frustrated by the influence of the pharmaceutical industry and

by questions of regulatory transparency. In particular, they remained frustrated by the inability to access adequate clinical trial data for SSRI antidepressants – one of the bestselling classes of drugs ever produced.

Conclusion

This chapter has focused on the size and scale of the domestic pharmaceutical industry, and on the specificities of the UK's drug regulatory system, in part to support my argument that a number of institutional factors hindered MHRA staff from acting swiftly on the evidence of the adverse effects during the controversy over the safety of SSRIs. In the next chapter, I provide a detailed analysis of this controversy. My focus on the specificities of debates over SSRIs is relevant for two main reasons. Firstly, questions surrounding the access, disclosure and interpretation of clinical trials for SSRIs serve as illustrations of problems surrounding RCTs in general. Secondly, my focus on the SSRI controversy – and on the individuals central to the controversy – enables me to explore the suggestion that medical practitioners are beholden to a moral authority of objectivity which bars them from voicing critiques of industry unless their dissent is restricted to the universe of numbers.

Chapter 4: SSRIs and the use of ignorance at the MHRA

The question is, then, whether there are circumstances that change the relationship between knowing and ignorance, perhaps to the point in which ignorance becomes the most important resource of action (Luhmann 1998: 94).

INTRODUCTION

When people ask Linda Hurcombe whether she has any children, she always replies that she has two: a daughter named Caitlin, and a surviving son named Sean. Her daughter, who she describes as a “normal, self-conscious, complicated teenager,” died by suicide on April 6, 1998, at the age of 19. At the time of her death, she had been taking a therapeutic regime of fluoxetine hydrochloride – more commonly known as Prozac. Hurcombe has since come to believe the drug was implicated in Caitlin’s suicide.

Five years after Caitlin’s death, Hurcombe published *Losing a Child*, a guide for helping other parents experiencing the sudden death of a child. In the book, she describes the last few months of Caitlin’s life. Caitlin, a happy, if at times volatile teenager, told her mother she wanted to take Prozac after a difficult Christmas season left her feeling down and upset with herself for gaining weight. She saw a doctor and was prescribed the medication. Caitlin kept Hurcombe posted of the decision, and together they read the *Patient’s Notes*, supplied by Eli Lilly, which included a leaflet entitled “Day by Day: A Guide to your first three weeks of treatment” urging patients to carry on taking the drug no matter how badly they felt.

Hurcombe describes how Caitlin, who had been depressed prior to taking Prozac, but rarely as manic as she became while on the drug, came to her one day

and said she had a recent series of nightmares where she killed herself. A couple of days later Caitlin said, “Mum, one thing I notice about being on Prozac is that like, I can’t cry even when I want to. I either feel like, calm and floaty like, or I feel like, massively angry, but in a calm sort of way.” Concerned, Hurcombe re-read the *Patient’s Notes*, and was reassured when they said not to worry if the patient was feeling extremely badly – as they remained on route to recovery as long as they kept taking the medication.

Caitlin began to act even more frenetically. She visited her brother Sean in London, and he suggested she not drink as much, especially while on Prozac. Back at home, her mother repeated the caution against alcohol. Her daughter said, “If you aren’t supposed drink alcohol while on the drug, the *Patient’s Notes* would say so, and there *is* no warning. You read the instructions out loud to me, Mum, remember?” (Hurcombe 2004: 5)

Caitlin’s mood swings deepened. During the last week of her life, her behaviour became frighteningly erratic. She carved the first initial of her boyfriend’s name on the back of her left hand, then rubbed a burn mark deep into the palm of her hand with the stub end of a pencil. Four days later, she wrote two suicide notes, and, slinging her childhood pony’s lunge rope over a wooden beam in the family’s guest bedroom, she hung herself. The post-mortem revealed only the presence of “fluoxetine hydrochloride (Prozac)” in her system.

In *Losing a Child*, Hurcombe describes how immediately following her daughter’s time on Prozac, she never thought the drug might have contributed to her death. Soon after Caitlin’s death, however, she began to question the safety of Prozac, leading her to meet with other parents and survivors who had lost their children while on SSRIs. Over the past fifteen years, numerous users have raised

similar questions as Hurcombe, asking whether SSRIs exacerbate the conditions they are intended to treat. Despite the growing number of individuals questioning the safety of SSRIs, Hurcombe and others have expressed frustration with the fact that they are still no closer to any clear answers.

This chapter provides an analysis of the regulatory processes that hindered the efforts of Hurcombe and others to reach conclusions on the medical risks and benefits of SSRI antidepressants. The focus of the chapter is on what I describe, drawing on Nietzsche, Niklas Luhmann and Michael Power, as a “will to ignorance” within regulatory bureaucracies which works to circumvent a regulator’s ability to carry out its outspoken aim or goal.

Firstly, I provide a history of the introduction of SSRIs to the UK market. Secondly, I suggest that the term “anti-strategy” is useful for understanding why regulators have done so little to address questions of SSRI safety even though they have had data indicating their potential dangers for over a decade. Finally, building on recent analyses of the political and scientific uses of ignorance, I develop a taxonomy of “strategic ignorance” in order to explore the value of uncertainty and ignorance to regulators.

Prozac nations: the rise of psychotropic cultures in the West

There would be no controversy over SSRIs had the drugs themselves not reached a significant level of popularity among consumers in Britain over the past fifteen years. In order to illustrate why the controversy carried such concerns for practitioners, regulators and patients, it is useful to give a description of the history and size of antidepressant consumption in Britain, placing the discussion of SSRIs within the broader context of the general post-WWII increase in the use of

psychotropic medications. Though accounts of why individuals are increasingly consuming psychotropic drugs often diverge, one thing is certain: consumption levels are increasing at a rapid rate, across all age groups and in all regions of the world. Data which Rose has derived from IMS Health, the World Health Organization and the International Narcotics Control Board indicates that over the decade from 1990 to 2000, the overall value of the psychiatric drug market increased by 126% in Europe and by 638% in the United States, where, by 2000, the value of sales of prescribed psychiatric drugs amounted to almost \$19 billion. In both the UK and the USA, the key growth area has been among antidepressants, with prescriptions of these drugs increasing by around 200% over the decade. In Europe, antidepressant prescribing rose at a rate of 50% across the decade (Rose 2006; Rose 2006; Rose 2006).

Increases in the consumption of psychotropic drugs are particularly marked among specific age groups, such as among children and adolescents in the US, Canada and Europe. A recent study from Brandeis University, which reviewed data on physician office visits across the United States, found that US prescriptions for the treatment of anxiety, depression and attention disorders in teenagers (aged 14 to 18) increased by 250% between 1994 and 2001. In particular, there were notable increases in prescription rates among teenage boys. During 2001, one in ten in all office visits by teenage boys across the country resulted in a prescription for a psychotropic drug. The study notes that the greatest general increase occurred in 1999, the year when direct-to-consumer pharmaceutical advertising became particularly widespread throughout the United States. The study adds that pharmaceutical companies increased their spending on TV advertising alone by a six-fold between 1996 and 2000, to a total of \$1.5 billion (Harper 2006; Thomas 2006).

The belief is sometimes expressed that the UK lags far behind the USA in psychotropic drug prescriptions to children. Though total sales still lag, a recent UK study illustrates that between 2000 and 2002, the percentage increase in sales of psychotropic drugs to children in the UK more than doubled that of the percentage increase in psychotropic sales in the USA (Wong 2004). The study used IMS Health data to track psychotropic drug prescribing for youth under 18 in nine countries (France, Germany, Spain, UK, Canada, USA, Brazil, Argentina, Mexico) between 2000 and 2002, and found that the number of prescriptions for children rose in all nine countries. The psychotropic medications investigated included antidepressants, stimulants, anti-psychotics, benzodiazepines and other anxiolytics. The highest percentage increase was in the UK (68%) while Germany had the lowest increase (13%). At 68%, the increase in the UK was more than double the percentage increase in the United States (30%) (Wong 2004).

As the above summary illustrates, the market for psychotropics has increased across all classes of drugs, from tranquilizers to anti-psychotics. Still, though, with perhaps the arguable exception of Ritalin, the psychotropic, mood-affecting drugs most well-known in North America and the UK today remain SSRI antidepressants such as Prozac and Seroxat. How did they reach their current level of popularity? The remainder of this chapter details their discovery and introduction to the British market, situating their emergence after two earlier classes of antidepressants: the monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants.

Psychopharmacological development of SSRI antidepressants

There are currently three main classes of antidepressant drugs available: Selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (see Figure 1).

Figure 1: Major Classes of Antidepressant drugs

(Source: Healy 2002a).

| Generic Drug Name | UK Trade Name | US Trade Name |
|---|-----------------------------|----------------------|
| Tricyclic antidepressants | | |
| Amitriptyline | Tryptizol/Lentizol | Elavil/Endep |
| Imipramine | Tofranil | Tofranil |
| Nortriptyline | Allegron | Aventyl |
| Protriptyline | Concordin | Vivactil |
| Desipramine | Pertofran/Norpramin | Pertofrane/Norpramin |
| Clomipramine | Anafranil | Anafranil |
| Dothiepin (dosulepin) | Protriaden | N/a |
| Lofepramine | Gamanil/Lomont | N/a |
| Doxepin | Sinequan | Adapin/Sinequan |
| Trimipramine | Surmontil | Surmontil |
| Monoamine oxidase inhibitors (MAOIs) | | |
| Phenelzine | Nardil | Nardil |
| Tranylcypromine | Parnate | Parnate |
| Moclobemide | Mannerix/Aurorix | N/a |
| Serotonin Reuptake Inhibitors | | |
| Citalopram | Cipramil | Celexa |
| Fluvoxamine | Faverin | Luvox |
| Fluoxetine | Prozac | Prozac |
| Paroxetine | Seroxat | Paxil |
| Sertraline | Lustral | Zolort |
| Venlafaxine | Efexor | Efexor |
| Other antidepressants | | |
| Bupropion | (Zyban – smoking cessation) | Welbutrin |
| Maprotiline | Ludiomil | Ludiomil |
| Mianserine | N/a | N/a |
| Mirtazapine | Zispin | Remeron |
| Nefazodone | Dutonin | Serzone |
| l-tryptophan | Optimax | Trofan |
| Reboxetine | Edronaz | N/a |
| Trazodone | Molipaxin | Desyrel |

In Britain, SSRIs account for half of all prescriptions for antidepressant drugs, of which a total of 26 million prescriptions were issued in 2003 (Morgan, Griffiths et al. 2005). An overview of developments in psychopharmacology in Britain and the US over the past 50 years helps to contextualize how SSRIs reached their current level of consumption.

One of the first widely used psychiatric drugs was chlorpromazine (a neuroleptic drug marketed as Largactil in the UK; Thorazine in the US), which was developed in the 1950s from antihistamines by Henry Laborit, a French military surgeon employed by Rhône-Poulenc. Unlike previous sedatives such as barbiturates, chlorpromazine was thought to act specifically on the symptoms of mental illness. The clinical effectiveness of chlorpromazine and other neuroleptic drugs produced soon after its appearance led researchers to try and identify their mode of action. Central to this was the discovery in the early 1950s of the presence of amines in the brain. Since then, a key effort of neuroscience and clinical psychiatry has been the refinement of experiments which have indicated that psychiatric drugs can be understood through a focus on the secretion, depletion and reuptake of amines in the synapses (Weatherall 1990; Healy 2002; Rose 2006).

In the early 1950s, for example, experiments with rats led researchers to hypothesize that chlorpromazine and related neuroleptics in some way blocked reuptake of the dopamine receptor, a finding that led to the construction of the 'dopamine hypothesis' as an explanation for the action of neuroleptic drugs (see Vrecko 2006). A similar hypothesis involving the biogenic amine system has been postulated to explain the efficacy of the family of drugs which appear to target the brain's serotonin receptor. These drugs have come to be known as the 'antidepressants.'

The first antidepressant is widely regarded to be a drug called imipramine. In 1950, Roland Kuhn, a psychiatrist working at the Münsterlingen Hospital in Switzerland began administering a derivative of iminodibenzyl (later called imipramine) to schizophrenic patients. Some became manic as a result, a surprising consequence which led to the idea that the drug had a euphoric effect. Kuhn set up a second trial in 1955, and published the results in a series of articles, such as an article in the *American Journal of Psychiatry* where he claims the imipramine was an 'antidepressant' efficacious in the treatment of endogenous, vital depression or melancholia (Kuhn 1958).

In 1952, it was found that two anti-tubercular drugs made by Hoffman-la-Roche – isoniazid and iproniazid – produced a euphoric mental effect in TB patients. Around the same period, Albert Zeller, a biochemist working at Northwestern University in the United States, published a paper with colleagues which suggested that iproniazid inhibited the monoamine oxidase enzyme in the brain. They noted that: "Since monoamine oxidase is considered to be an important agent in the activation of adrenaline and noradrenaline, this strong inhibition may be connected with some side reaction produced by this drug' (Zeller et al 1952, quoted in Rose 2006c).

In 1956, George Grane published a paper which reviewed the psychiatric side-effects of iproniazid, now marketed by Roche under the name Marsalid, and in 1958, Nathan Kline, a pioneer in the field of psychopharmacology, suggested iproniazid was a "psychic energizer." Rose points out a number of different researchers contributed to the discovery of iproniazid's antidepressant effects. Taken together, the contributions of these disparate researchers and clinicians, together with developments surrounding the neuroleptics and other psychotropics, helped to usher

a new style of thought in psychiatry which suggested that the origins of mental disorders were to be found in the biochemical workings of neurotransmitters such as serotonin, norepinephrine and dopamine (Rose 2006c; Vrecko 2006).

Until the late 50s and early 60s, the perception that drugs such as imipramine and iproniazid seemed to alleviate symptoms of depression stemmed from clinical observations. There was, in the late 1950s, no specific understanding of mode of actions of these drugs – no clear idea of which neurotransmitter they were potentially affecting in the brain. Indeed, serotonin (also referred to as 5HT) had yet to be implicated in the course of an antidepressant's action. This began to change in the late 1950s, when a number of researchers published studies which sought to make links between clinical observations and biomedical activity. The most significant early article was published by Pare and Sandler in 1957. They asked the question of why iproniazid had euphoric effects, and suggested the answer lay in the fact that iproniazid inhibits monoamine oxidase, the enzyme that activates the serotonin (5HT) neurotransmitter and other naturally occurring amines in brain (Rose 2006c).

This suggestion from Pare and Sandler is one of the first intimations of what has come to be known as the serotonin hypothesis of depression, or the idea that lowered levels of serotonin are implicated in the onset of depressive symptoms. A next step in the formulation of this hypothesis was a 1965 paper by Joseph Schildkraut called "The catecholamine hypothesis of affective disorders: a review of supporting evidence," published in the *American Journal of Psychiatry*. In the article, Schildkraut argues that depression is associated with low levels of catecholamines (the group of neurotransmitters that includes serotonin) in the brain. Since the publication of Schildkraut's paper, much psychopharmacological research has sought to prove the serotonin hypothesis of depression – the idea that depression

is caused by a lack of sufficient serotonin levels in the brain. Thus far, no research has established conclusive evidence of this hypothesis, and scientists remained divided over the question of whether lowered serotonin is at root in depression. (Healy 2004; Lacasse and Leo 2005).

Despite this lack of consensus among scientists, many members of the public in Britain and the US continue today to equate depression with ideas of serotonin imbalance. This gap between public and scientific understandings of depression has been central to the success of marketing campaigns for the class of antidepressants that have been specifically manufactured and marketed as bullets which select and target the transmission of serotonin in the brain: The selective serotonin reuptake inhibitors (SSRIs).

Battles for market authority: The marketing of SSRIs

During the mid-1960s, a neuroscientist named Arvid Carlsson began to work on the development of a class of drugs that would particularly target the serotonin system. In the early 1970, while employed by Astra (now called Astra-Zeneca), he applied for a patent for zimelidine (Zelmid). The patent was awarded in 1972, two years before Eli Lilly was granted a patent for Prozac. Astra then signed an agreement with Merck to market Zelmid in the United States, and, as David Healy writes, had the agreement proceeded, the Prozac phenomenon might not have occurred. But, just as data on Zelmid was being considered by the US Food and Drug Administration (FDA), evidence emerged that Zelmid could provoke the onset of the neurological disorder Guillain-Barré syndrome. As a result, Zelmid was removed from the market (Healy 2004).

The first SSRI introduced to the British market was fluvoxamine, marketed as Luvox in the United States and Faverin in the UK. It appeared in 1988, and was closely followed in 1989 with the introduction of fluoxetine (Prozac). A 1990 article from the *Drug and Therapeutic Bulletin*, an industry newsletter about drug safety which is widely read by British medical professionals, notes that, particularly as Prozac had been ‘hyped’ in a recent *Newsweek* article, a critical examination of the drug was warranted. The article offers the following conclusion on Prozac’s efficacy:

Fluoxetine joins the ranks of several new antidepressives that are similar in efficacy to conventional tricyclics, but appear to have fewer unwanted effects. It has not been compared with the newer tricyclic and related antidepressives. There is no evidence that it acts quicker than other antidepressives or that it is effective in patients who do not respond. Fluoxetine may cause anorexia rather than stimulate appetite like other antidepressives and may therefore have a place in the treatment of obese patients with pathological depression. However, it is unsuitable simply for fat, sad people who despair of losing weight (DTB 1990).

The above comment comes two years before the UK’s Royal College of Psychiatrists launched a “Defeat Depression” campaign aimed at raising more sensitivity among practitioners in identifying and treating depression (such as avoiding, one somewhat hopes, the suggestion that a patient is simply too fat or sad for treatment).

Lundbeck’s Citalopram, marketed as Cipramil (UK) and Celexa (US), was developed in the early 1970s and introduced to the US market in 1998. During the late 1990s, Celexa had a similar profile and popularity to Pfizer’s Zoloft, which first hit the US market in 1992, and is today the world’s best-selling SSRI. During the 1990s, both Zoloft and Celexa were second in profile and popularity to the largest-selling and most well-known SSRIs: Prozac and Seroxat (marketing as Paxil in the US).

Seroxat was introduced to the British market in 1991 by SmithKline Beecham. David Healy, a well-known scholar of psychopharmacology and one of the first to suggest that SSRIs produced adverse effects in some users, notes that it was actually marketers within SmithKline Beecham who coined the term “SSRI.” They argued that compared to earlier antidepressants, Seroxat was a more ‘selective’ therapy, targeting the uptake of serotonin more directly. The name was later extended to the other compounds in the class (Healy 2004: 27). Though Seroxat has performed well financially, revenues paled in comparison to the most celebrated of SSRIs: Eli Lilly’s Prozac, for which the patent expired in 2001. In the years leading up to 2000, Prozac generated about \$2.6 billion for Eli Lilly annually, a full quarter of the company’s total revenues (Shook 2000).

How to account for the phenomenal popularity of SSRIs over the earlier and less expensive classes of antidepressants? There are a number of explanations. One is the influence, during the period of the introduction of the SSRIs, of a widespread controversy surrounding the safety of a different class of psychotropic drugs – benzodiazepines such as Halcion which were shown to cause dependency in some users and which were, in the case of Halcion, removed from the British market (Abraham and Sheppard 1999). Because of concerns that many patients were becoming dependent on benzodiazepines, there was a need to find a safer psychotropic alternative. My interviews with British medical practitioners make clear that that alternate was thought to lie with the SSRIs, the safety of which was assured by a number of sources, such as the Royal College of Psychiatrists. As one primary-care practitioner noted in an interview with me, while recalling factors surrounding the clinical popularity of the SSRIs in the early 1990s:

The other issue was around this anxiety about the benzodiazepines being found to be addictive...the [Royal College of Psychiatrists’] Defeat Depression

campaign was a conscientious attempt to raise awareness among GPs that there were all sorts of people with clinical depression out there. That depression was an illness. That it had to be treated properly. And that the drugs weren't addictive. That was the message of the Defeat Depression campaign [LM interview with Timothy Fox, May 2005].

Rose's data on prescribing trends in Britain supports the observation of a correlation between declining benzodiazepine prescriptions and increasing SSRI sales. Between 1980 and 2000, the total number of prescriptions dispensed in the four main classes of psychiatric drugs – hypnotics and anxiolytics (which include benzodiazepine); anti-psychotics; antidepressants; and stimulants – rose at a growth of about 30%. This growth, however, disguises the fact that between 1980 to 1994, the total number of prescriptions actually declined – something owing to a decline in prescriptions for minor tranquillizers and benzodiazepines. In general, between 1980 and 2000, prescriptions for anxiolytics (including benzodiazepines) declined by about 32%. Meanwhile, the same period saw a 200% increase in antidepressant prescriptions (Rose 2006). Fears surrounding benzodiazepine safety can not entirely explain, however, why there were such substantial increases in SSRI prescribing by British GPs and practitioners throughout the 1990s. They can not explain, for example, why SSRIs were increasingly prescribed over earlier (and far less expensive) classes of antidepressants – the tricyclics and MAOIs. And they can not explain why there were increased diagnoses of the disorder of depression in the first place.

As for the question of the popularity of SSRIs over tricyclics and MAOIs: the short answer is that SSRIs appeared initially to have few of the dangerous side-effects associated with MAOIs and tricyclics. MAOIs were found very early on to produce numerous side-effects such as fatigue, nausea, sleep disturbances, drowsiness and sexual dysfunction, as well as life-threatening reactions in some

patients when consumed with certain foods, such as cheese and yeast extracts. This led to their diminished popularity next to tricyclics. Tricyclics, meanwhile, have a higher toxicity level than SSRI, which makes it much easier for patients to accidentally or deliberate overdose on tricyclics than on SSRIs. One of the practitioners I spoke to touches on the problem of safety in overdose – and alludes to wider social factors which contributed to the prescribing of SSRIs over tricyclics:

SD: The political bit actually came in when the other SSRIs started to come out. [Leading psychiatrists] jumped on the bandwagon, 'saying not toxic in overdose.' Which is true. Okay? That's true. But they avoided the perspective of how many killed: is this going to reduce the suicide rate? The sociological aspect of this is that if you ask a young psychiatrists about tricyclics they say, "I wouldn't give one to my dog." So, they've been, not brainwashed, but persuaded that SSRIs are the way to go.

LM: Were there many political considerations (among those advocating SSRIs)? Were they just simply convinced of the medical efficacy?

SD: There were covert threats, which I thought was awful, in the press, which said that if a doctor now prescribes a tricyclic, and that patient overdoses on a tricyclic, then the doctor should be prosecuted for negligence. That terrified everybody (LM interview with Stuart Donovan, clinical epidemiologist, February 2005).

If levels of toxicity can explain the preference for SSRIs over tricyclics, what factors might explain the general increase in prescriptions of antidepressants in the first place? A number of sociologists have addressed this question (e.g. Healy 2004; Rose 2003; Martin 2004; Lakoff 2004; Fraser 2001, 2003), identifying cultural, economic and political factors which have led to the dramatic increase in prescription rates. They note factors such as, first, industry efforts to promote and sell the idea of depression in order to bolster the antidepressant market. Second, the influence of professional bodies such as the Royal College of Psychiatrists, and their efforts to promote awareness through campaigns such as Defeat Depression. Third, the influence of popular works such as Peter Kramer's *Listening to Prozac* (1997), Lauren Slater's *Prozac Diary* (1998), and Andrew Solomon's *The Noonday Demon*:

An Atlas of Depression (2001), which helped to diminish some of the cultural stigmatization surrounding mental illness.

Regardless of the conflicting explanations for the popularity of SSRIs, one thing is certain. Over the last ten years, SSRIs have reached unprecedented levels of use within British society. It is possible that the high volume of their use can help to account for how individuals have responded to the recent debates over the suggestion of their dangerous side-effects. Cultural acceptance of the safety of psychopharmaceutical drugs – “safety” in both a practical sense, as in having an acceptable risk/benefit profile, and in a symbolic sense, as in carrying lesser danger of public stigmatization for their use – might have contributed to the depth of public surprise and anger when, in the case of SSRIs, suggestions arose of their possible lethality. Drawing on interviews with practitioners, the next section addresses such questions, by looking in more depth at the emergence of the controversy over the safety of SSRIs.

Was the depression or the medication at fault? Dilemmas at heart of debates over SSRIs and suicide

Since their introduction to the British and North American market, three different charges have been levelled against SSRIs. Firstly, that they lead to suicidal and homicidal thoughts and actions in some users. Secondly, that they lead to withdrawal symptoms, and should therefore be considered drugs which cause dependence. Thirdly, that the drugs have not been shown to be more efficacious than placebo in treating depressive disorders. This trio of complaints surrounding SSRIs has spurred thousands of articles, studies and reviews from hundreds of psychiatrists, health analysts and patients. Given the breadth of attention, this thesis is focused on just one aspect of the debate: the question of whether SSRIs lead to suicidal or

homicidal thoughts and actions in some users, and the UK regulatory response to such questions.

This question turns on a fundamental dilemma which has made it difficult to determine whether the drugs contribute to suicide: how can one determine whether it was the drug, or the underlying depression for which the drug is intended to treat, that led a person to take his or her life? This problem is typical of efforts to prove drug-related injury with many pharmaceutical drugs, where often “drug reactions may mimic the disease they are supposed to be treating” (Corrigan 2002: 501). This problem is compounded by the fact that, as Oonagh Corrigan writes, if a doctor thinks an adverse reaction is the result of a worsening condition, they may not report the event as possibly drug related.

In general, adverse effects are detected during pre-clinical testing and during post-market surveillance, where both agencies such as the MHRA and companies which hold a licence are legally culpable for monitoring a drug’s effects once it is on the market (Abraham 1995; Corrigan 2002; Abraham and Smith 2003).

The clinical stage of testing a drug generally takes place over four phases. Phase I trials typically involve healthy volunteers, usually between 100 and 200, and are designed to test the tolerability and safety of a drug. Initially, single doses of the drug are given to participants. Repeated doses are then given, and the safety is compared to results from animal studies. This phase also determines the dosage for subsequent trials (HOCa 2005). If the product appears safe, testing proceeds to Phase II, which typically takes place in a hospital setting, carried out by clinical investigators such as doctors. Generally, 250-500 patients are involved at this stage, which is primarily concerned with establishing the optimum dosage of the drug in sick patients (Corrigan 2002: 500).

Phase III trials involve larger groups of patients, usually about 2,000 to 3,000 (with smaller cohorts if a condition is a rare disease), and are intended to determine the safety and efficacy of the drug on a larger scale, either by comparing the product to a drug that is already on the market to treat the target condition or to a placebo (HOCa 2005). Phase IV clinical trials are conducted once a product already has a licence, and are carried out for a range of reasons, such as to determine adverse effects, or to determine efficacy in a population not previously studied during the pre-market phase, such as in children or the elderly (Corrigan 2002). When a manufacturer seeks licensing approval, it is required by UK law to MHRA all clinical (and non-clinical) studies relevant to the safety and efficacy of a drug, but it usually highlight the studies central to its case for approval (Abraham 2007).

As has been widely noted by scholars of drug regulation, there is much uncertainty about how to extrapolate from animal studies and pre-market studies in humans, to the wider clinical environments in which drugs are used once they are approved by a regulatory body (Abraham 2002; Abraham 2007). This uncertainty has been fundamental to the difficulties of determining SSRI safety, as well as to the question of whether the MHRA failed to publicly disclose the adverse effects of SSRIs when they first learned of them.

Alongside the challenge noted earlier – the fact that suicidal behaviour is a key symptom of the condition that antidepressants are intended to treat – David Nutt, a well-regarded professor of psychopharmacology at Bristol, has described three aspects of the relationship between depression, antidepressant drugs and suicide that make it hard to determine the role of SSRIs in contributing to suicidal thoughts and acts. Firstly, all antidepressants, as a result of their toxicity levels, can be fatal if taken at too high a dosage, and thus Nutt suggests SSRIs are no

more dangerous than earlier classes of antidepressants such as tricyclics. Secondly, during recovery from depression, suicidal risk often increases as people become more “energized” and more motivated to carry out the act of suicide – thus it is hard to determine whether a drug, or the emergence from a deeper state of lethargy or inertia, is responsible for an individual having adequate energy to commit suicide. Thirdly, all antidepressants, including SSRIs, can cause agitation and activation at the start of treatment, something which is characterised by the emergence or the worsening of insomnia, and feelings of restlessness and intense anxiety. Nutt stresses that these adverse reactions are widely reported and well-known side-effects of all antidepressants. The question is therefore whether the benefits of SSRIs in reducing depression outweighs their potential detriment in causing certain adverse effects that might contribute to suicide (Nutt 2003).

It is on this last point that Nutt, who argues on balance that SSRIs are safe and beneficial drugs, differs from Healy, who has become publicly well-known in Britain and around the world for his outspoken views on the link between SSRIs and suicide. One of Healy’s central arguments turns on the fact that the majority of patients treated with SSRIs have only mild or moderate depression – a category where patients are believed to have a relatively low risk of suicide if they do not receive treatment. Thus the use of SSRIs, drugs which are proven to cause agitation in some users, unnecessarily exposes them to a greater risk of suicide (Healy 2004).

Explained in the terms above, the debates over SSRIs and suicidality seem fairly straightforward, and certainly, given enough scrutiny from scientists and regulatory authorities in the US and the UK, something that could be resolved over time. It seems only logical, for example, that in seeking to investigate Nutt’s question of whether the benefits of using SSRI outweigh the detriments, one need only turn to

epidemiological studies of SSRI use among specific populations and geographical regions and to ask whether suicide rates dropped since the introduction of SSRIs. The problem is that for every epidemiological study indicating lowered suicide rates in one region, there are separate studies suggesting escalating rates in regions (See for example Gibbons 2005; Licinio and Wong 2005; Morgan, Griffiths et al. 2005). Also, suicide figures often differ dramatically among different demographic groups in any given population. As David Gunnell, a leading British epidemiologist, explained to me during an interview in June 2005:

In Britain, suicide rates over the last 100 years have halved. Remember that over the last 50 years there have been quite striking fluctuations in suicide rates. Suicide rates in young men have doubled. Suicide rates in older men have, since the war, halved or more. And those big effects aren't due to the effects of antidepressant treatment because antidepressant treatment wasn't around in the 1940s or 50s. We don't know for sure what underlies the decline in suicide since the 1950s in older men. There are a number of speculations about it. But we don't know for sure. And unless you can model all those factors into an equation to control for them, and then look at any possible independent effects of antidepressants, we are not going to get a clear answer (LM interview with David Gunnell, Professor of Epidemiology, Bristol University, June 2005).

David Healy's suggestion – that SSRIs lead to agitation and increased thoughts of suicide in patients who might otherwise not have demonstrated any suicidal tendencies – seems most effectively investigated by examining the randomized controlled trials testing SSRIs in patients and determining whether there have been increased incidences of suicidal thoughts, impulses and completed attempts among patients randomized to SSRIs as there have been among those randomized to the control treatment. One of the problems facing such efforts is that in the past manufacturers such as Eli Lilly and GlaxoSmithKline have suppressed, whether accidentally or deliberately, the results of clinical trials which have indicated more patients experienced suicidal ideation and actions while on SSRIs than those on

placebo, thus rendering it difficult for regulators to gain a comprehensive understanding of all available data on SSRIs (Kondro 2004; Lenzer 2006).

In the next part of this chapter, I continue to introduce the individuals, such as Healy, who have been central to the emergence of questions over SSRI safety. Two things in particular are of theoretical significance. The first is that the debates over SSRIs illustrate the professional repercussions when individual practitioners choose to publicize their private concerns over commercial or political influences on medicine. Throughout the controversy over SSRI, practitioners such as Healy have been vilified both professionally and personally for casting doubt on the scientific validity of what was perceived among dominant medical authorities as the established evidence of SSRI safety. I argue that the public condemning of Healy and others suggests there is an onus to maintain the appearance of impartiality lest they lose their professional stature and the approval of their peers.

This onus of impartiality carries particular ramifications when one considers that the commercialization of medicine through things such as the pharmaceutical industry's funding of regulatory bodies has led to a situation where collaborations with industry are the *de facto* norm in science and medicine. Thus any personal critique of industry is a step outside of what is perceived as the current status quo in medicine. If one disparages the influence of industry, one risks one's perceived impartiality.

Secondly, I argue the SSRI controversy illustrates something that Power has noted of the financial audit (Power 1994; Power 2003), which is how during times of financial scandal, whenever the accuracy of individual audits is called into question, the solution is to call for more audits. Very rarely is attention drawn to how the process of auditing is flawed in the first place. The same reluctance to look beneath

the “opacity of process,” to use Power’s phrase, occurs during crises over drug safety. During the SSRI controversy, whenever individual RCTs indicated problems with SSRIs, the answer has typically been to call for more RCTs. Little attention has been focused on what is arguably the largest obstacle surrounding efforts to investigate SSRI safety: the relationship between regulators and pharmaceutical companies, and the fact that companies have an obvious incentive in not disclosing all clinical trials, and that regulators have an equally obvious interest in not revealing the ways they might be ineffective at regulating drugs. It was one of my informants who first called my attention to this problem:

In the case of antidepressants, [the MHRA] conducted no fewer than six inquiries before finally establishing an independent inquiry which established that things were indeed wrong. [This raises a] point about the conflict-of-interest that arises when one and the same body is responsible for pre-marketing approval and post-marketing surveillance. The point being that if you discover problems with the drug you have probably also discovered some regulatory oversight. Therefore are you going to admit a liability? Or are you going to keep your head down? The answer is, so far as I can see, the regulator just keeps its head down (LM interview with Charles Medawar, a health policy lobbyist, March 2005).

The informant raises a simple but remarkably under-acknowledged point. When the same agency is responsible for both the pre-licensing approval of drugs, and the post-marketing surveillance of their use, the discovery of significant adverse effects calls attention to the possibility of regulatory negligence in approving them in the first place. Though the approval of any drug carries a certain degree of risk, as its full clinical effects are often unclear until one can gauge its performance over time, licensing a drug which carries *severe* adverse effects risks a degree of public mistrust over the regulator’s competence in approving the drug in the first place – particularly when those risks are detectable in pre-licensing clinical trial data. Silence on the part of the regulatory agency may become a survival tactic (McGoey 2007).

Obvious as this comment seems, that regulators have clear motives for seeking to obscure their own mistakes, only recently have social scientists paid much attention to the implications of such a tactic, to explore the possibility of a strategic “will to ignorance” within bureaucratic organizations such as the MHRA, or the idea, as Hutter and Power put it, drawing on work by Weick and Turner, that organizations may be “defined in terms of what their members chose to ignore” (Hutter and Power 2005: 18).

Although some have recognized how the need to discount information contrary to an organization’s prevalent ethos or worldview often lead individuals to omit “the very information they were meant to catch” (Weick 1998: 74), little attention has been paid to the role of ignorance in maintaining institutional efficiency. In the case of the SSRIs, a better understanding of the incentives for cultivating a strategic ignorance help to illuminate why regulators have done relatively little to flag concerns surrounding the drugs though they have had access to data suggestive of their adverse effects for over a decade.

On the existence of anti-strategies within bureaucracies

Obviously, the suggestion that regulators have an incentive in concealing data from the public is hardly new. As Weber, the seminal theorist of bureaucracy observed years ago, secrecy lies at the heart of bureaucratic authority (see for example Weber 1922 (1995); Weber 1978). What is new, however, in part as a result of things such as the adoption of Freedom of Information legislation in the United States and Britain, is the increased demand for regulatory and bureaucratic transparency, and with it the need for more resourceful strategies of non-disclosure. A strategy of ignorance – whether adopted deliberately or unconsciously, collectively

or individually – answers the twin demands of appearing transparent while wielding control over the very information one has an interest in concealing.

In *Society Must be Defended*, Foucault calls attention to the battles of knowledge that took place in Europe during the eighteenth century, to the use of a “perspectival and strategic truth” among those attempting to answer the increasing demands of governing through the tropes of freedom versus control or domination (Foucault 2003 (1975): 268). Foucault notes that at the heart of such eighteenth-century struggles was the battle to establish a dissymmetry in access to knowledge; at stake was the “matter of establishing a truth that functions as a weapon” (2003: 169).

Where Foucault identified the use of a strategic truth, one might suggest the opposite, yet complementary trope of strategic ignorance. Today, as inequalities in access to information face increasing scrutiny, as people argue for a levelling of informational battlefields through freedom of information legislation, and through the distribution of technologies such as open-source software, it is possible that ignorance – wielded as a strategic weapon – provides solutions to a problem unique to democracies which place a premium on public access to governmental information. Strategic ignorance allows those in authority to deny knowledge of the truths which they are increasingly expected to share.

Applying the concept of strategic ignorance to specific empirical examples, such as the case-study below of the MHRA’s handling of the SSRI controversy, might help to modify the tendency to assume an *a priori* natural rationality and functionality of bureaucratic decisions. The oxymoronic quality of a phrase like strategic ignorance helps to remind of the opposite, to the incentives in purposefully perpetuating irrational acts. It illuminates the fact that many bureaucratic decisions are either illogical, or carry a tacit logic contrary to any outspoken aims. The

heuristic of ignorance helps to illustrate the at times systematic absurdity of bureaucracy.

Despite the fact that some sociological analyses of organizations and bureaucracy have paid detailed attention to questions of the absurdity versus rationality and functionality of bureaucratic decisions (for example Blau 1956; Crozier 1964; DiMaggio and Powell 1983), much work in this area has remained wedded to the notion of bureaucracy's innate rationality. Many attribute this notion to Weber, despite the fact that Weber did not assert bureaucracies were inherently rational, only that their legitimacy rested on their claims of rationality. Recent analyses of bureaucracy such as those collected in *The Values of Bureaucracy* (2006), edited by Paul du Gay, have often fallen into two broad camps. In the first, bureaucracies are seen in practice to rarely reflect ideals of rationality and efficiency, leading observers to doubt the empirical usefulness of Weber's observations.

The opposite concern is that bureaucracies are overly functional, producing an excess of conformity and uniformity among administrators, and enforcing an ethos of impersonality that renders creativity impossible. This second criticism often turns on the fear, to quote organizational theorist Michael Reed, of the tendency of "bureaucratic organizations to exceed their instrumental or technical role and to acquire unaccountable political power and influence" (Reed 2005: 121). Whether in doubting the ability of bureaucracies to render the efficiency they purport, or, conversely, in raising concerns of the consequences of a systematic drive toward all-encompassing efficiency, there remains a shared faith in the existence of certain indelible features, such as rationality, efficiency and impartiality (see du Gay 2005).

Even in the work of Foucault, despite his emphasis on epistemic disjunctions and the vitality of error, there remains an assumption of the functional nature of

bureaucracies, a belief, such as in his discussions on the panopticon, in the bureaucratic structure's inherent success in engendering the control which it seeks. At a recent lecture, the anthropologist David Graeber summarized this faith shared equally by Foucault and Weber when he quipped of the two, "It's no coincidence that these sometimes appear to be the only two intelligent people in human history who honestly believed that bureaucracies work" (Graeber 2006: 4). The comment was meant only slightly facetiously. Graeber elaborated:

Weber saw bureaucratic forms of organization as the very embodiment of rationality, so obviously superior to any alternative that they threatened to lock humanity in a joyless "iron cage" bereft of spirit and charisma. Foucault was far more subversive, but in a way that made bureaucratic power more effective, not less (2006: 4).

Divergences from natural functionality are viewed as an anomaly, as an aberration of correct procedure, rather than endemic to the system itself. The detection of an irrational or an illogical act, such as carrying out an inquiry into a pharmaceutical drug's safety and then burying any evidence of harm, is viewed as an isolated example of dysfunction. In situations where the inquiry's failure is widely recognized by the public, attracting a measure of scorn to whatever bureaucratic body launched the hearing to begin with, the answer is simply to call for more inquiries.

Power has drawn attention to a similar cyclical phenomenon: "Audits," he notes, have a "remarkable capacity of being invulnerable to their own failure" (Power 1994: 7; see also Power 2003). When attention does occasionally turn to the process, individuals are typically blamed instead of the circumstances in which they worked. As Power notes, "in the wake of scandals and frauds, audit failure is usually located as a *particular* problem of fraudulent management or credulous auditors and is addressed by extensive *codification* of new official audit guidance. The principle

seems to be that the general efficacy of audit must be preserved if the reputation of particular practitioners is not" (Power 1994: 30).

Power's work contains a number of insights relevant to the analysis of drugs regulation in Britain. He notes, for example, that a curious result of the intensification of auditing procedures and the codification of new rules following a corporate scandal is that knowledge generally become more expert and more inscrutable, and therefore less accessible or accountable. Yet, paradoxically, through the launch of yet another inquiry or through the introduction of new rules, the illusion of transparency is strengthened; people sigh in relief over the observation that at least something is being done.

It is this invulnerability of system that has perhaps blinded observers to a more nuanced analysis of why regulatory hearings so often fail to produce the findings which they have seemingly set out to uncover. The remedy for this myopia must begin with a reversal of core assumptions. It demands a suspension of trust, a dismissal of any *a priori* assumptions of the regulatory structure's inherent functionality to begin with. Though I have suggested Foucault shares with Weber such *a priori* assumptions, it is from Foucault that a more nuanced analysis of regulatory interest can be drawn, and specifically from his work on the unexpected consequences that often arise from situations of bureaucratic, administrative or legal control.

One example, as the anthropologist James Ferguson describes, appears in Foucault's genealogy of the prison system, where Foucault points out that despite the prison's origins as a correctional institution meant to rehabilitate criminals and reduce criminality, it is apparent that, on the contrary, rather than decrease criminality, prisons manage to intensify it. While this result represents a failure from

the perspective of early planners' explicit intentions, the result has a different character when perceived as part of a different, implicit strategy. By producing a well-defined class of delinquents, readily identifiable among the public as warranting imprisonment, prisons do end up serving as part of system of disciplinary control, but in a different way than the planners had envisioned (Ferguson 1990). As Foucault describes, the prison system creates an unintended outcome, an "unforeseen effect which had nothing to do with any kind of strategic ruse on the part of some meta or trans-historical subject conceiving and willing it" (Foucault 1980: 195).

From the concept of unforeseen and unintended effects I wish to suggest the converse, yet complementary, concept of *anti-strategy*. An anti-strategy is the tacit pressure at root in any regulatory process, inquiry or hearing which works to contradict the outspoken aim or goal of the inquiry. In the case of the MHRA's many inquiries into the safety of SSRIs, the anti-strategy, as I argue in more depth below, has been two-fold. Firstly, the commercial need to maintain positive relations with the pharmaceutical industry funding the MHRA's operations. Secondly, the need to retain public trust in the agency's competency. Those two demands hindered the MHRA's ability to carry out its explicit goal: arbitrating on the safety of drugs and removing from the market any drugs indicated to carry more risks than benefits.

MHRA staff might resent the suggestion that they deliberately misinterpreted or suppressed clinical trial data in order to help ensure their organization's monetary sustenance and public reputation. To most, such deliberate actions are unthinkable. Which, I suggest, is the point. Drawing on work by Nietzsche and Foucault, I suggest that anti-strategies are typically (but not always) unarticulated phenomena, creating constraints that remain indefinable even to the individuals who are subject to them.

Of course, Foucault's notion of unforeseen and unintended events is not novel. As the sociologist Diane Vaughan notes, Merton was one of "the first to observe that any system of action can generate unexpected consequences that are in contradiction to its goals and objectives" (Vaughan 2005: 33). The concept of anti-strategy seeks to complement the idea of unexpected consequences by focusing not on effects, but on *unarticulated strategies*. In line with work by Turner, it stresses that often it is implicit institutional needs, and not simply consequences, that are in contradiction with an organization's outspoken goals and aims. The two are distinct yet interrelated, as unintended effects often stem from the influence of unarticulated strategies.

These points are influenced by Nietzsche's argument in *Beyond Good and Evil*, where he argues philosophers, misguided by a "morality of intentions," have paid too much attention to the conscious and the articulated, ignoring the influence of unconscious motives on the unfolding of events:

a peculiar narrowness of interpretation therewith became dominant: men interpreted the origin of the action in the most definite sense as origin in an *intention*; men because *unanimous* in the belief that the value of an action resided in the value of the intention behind it...the morality of intentions has been a prejudice, a precipitancy, perhaps something provisional and precursory, perhaps something of the order of astronomy and alchemy, but in any event something that must be overcome (Nietzsche 1990 (1973): 63-64).

It is debatable whether Foucault accepts or rejects Nietzsche's assertion of the importance of the unconscious. Deleuze, for example, in his analysis of Foucault, paints an image of someone who has rejected completely the emphasis on things which can not be consciously asserted: "That everything is always said in every age is perhaps Foucault's greatest historical principle: behind the curtain there is nothing to see, but it was all the more important each time to define the curtain, or the base, since there was nothing hidden or beneath it" (Deleuze 2006 (1988): 47).

At first, Deleuze's insight raises a contradiction. How can Foucault, the very scholar who has stressed the importance of the unintended and the unforeseen, be the same one to argue that *nothing* is unsayable, to argue that even the most unimaginable of statements can be deciphered from the discourse of those in authority, if only one knows where to look? Deleuze adds a caveat that helps to unravel this contradiction: "statements become readable or sayable only in relation to the conditions that make them so...the subject is a place or position which varies greatly according to its type and the threshold of the statement, and the 'author' himself is merely one of these possible positions" (1988: 47).

Foucault's assertion that the conscious actions of individual authors are intelligible only through an understanding of their institutional milieu is what reconciles his thought to Nietzsche's assertion that conscious thoughts are "insignificant" in comparison to the interrelation of countless events that occur in every instance. Together, their work helps to remind that often the most profound outcomes result not from individual decisions, but in spite of them, unwittingly resulting from the action of players who remain blind to the secondary implications of their actions. Related to this, just as statements become comprehensible "only in relation to the conditions that make them so," the *silence* of an individual in refusing to admit information contrary to the worldview of an organization is often comprehensible only in relation to the conditions that make it difficult to speak.

It is the tacit, unarticulated nature of anti-strategies that makes it easier to dismiss regulatory malfunctions as simply the result of human fallibility or human idiocy, rather than the result of systematic institutional pressures. Error and ignorance have so long been thought of as antithetical to the pursuit of truth and knowledge that to realize that errors might be perpetuated on purpose, that a

regulatory body might systematically and purposefully conduct faulty inquiry after faulty inquiry in order to serve a more implicit interest, at first strikes as absurd.

Even among those familiar with Popper's assertion that science is strengthened by the admission of error, that science must prove its own fallibility in order to distinguish itself from pseudo-science, there remains a refusal to acknowledge the pervasiveness of error and malfunction. We remain immersed in epistemes of the will to truth and the will to power, overlooking that Nietzsche postulated a "will to ignorance" as preceding these more celebrated two.⁶ In order to grasp why the MHRA remained blind for long to the information for which it was ostensibly looking, one must dispel the automatic equivalence of knowledge as power and realize that in cultivating a strategic ignorance – in refusing to admit even that one harbours a secret – one often wields the most strength. But where is the evidence for these assertions? A detailed analysis of the SSRI controversy helps to illuminate one example of the "will to ignorance" in practice.

SSRIs throughout the 1990s: From disbelief to demands for government inquiries

Debates over SSRIs and suicidality were initiated in 1990, when Martin Teicher, a psychiatrist at Harvard University, published a study in the *American Journal of Psychiatry* which outlined six cases where patients experienced suicidal thoughts while on Prozac (Teicher, Glod et al. 1990). Eli Lilly, the manufacturers of Prozac, countered with a meta-analysis from Charles Beasley (Beasley, Dornseif et al. 1991), which examined clinical trials involving 3,065 patients, 1700 of whom had

⁶ In *Beyond Good and Evil*, Nietzsche raises the question of why there has been a historical and theoretical privileging of truth over ignorance: "Granted we want truth: *why not rather untruth?* And uncertainty? Even ignorance?...To recognize untruth as a condition of life: that, to be sure, means to resist customary value-sentiments in a dangerous fashion; and a philosophy which ventures to do so places itself, by that act alone, beyond good and evil" (Nietzsche 1973: 33-36).

been randomized to Prozac, and which found no evidence for increased suicidal thoughts among those on Prozac. David Healy has pointed out a number of methodological problems with the Beasley study, such as the fact that only 3,067 patients of the approximately 26,000 patients entered into clinical trials of fluoxetine were included in the final meta-analysis, and secondly, there was joint prescription of benzodiazepines in the clinical trial program in order to minimize the agitation caused by Prozac (Healy 2004).

The Teicher study, as well as anecdotal clinical reports of adverse patient reactions to Prozac, led the FDA in the United States to convene, on September 20, 1991, a special hearing of the Psychopharmacological Drugs Advisory Committee (PDAC) in order to investigate the question of Prozac and suicidality. The transcripts of that hearing – emerging as they do some 13 years before the FDA chose to issue a black box warning on SSRIs – serve as prescient reading today. Despite hearing some 110 pages of oral reports from parents of children and other family members who harmed themselves or committed suicide while on Prozac, and despite hearing from psychiatrists such as Teicher who testified about his concerns over the safety of Prozac, the PDAC committee voted against the implementation of any label change that might advise physicians of the scientific uncertainty over the safety of the drug (FDA 1991).

Mariam Fraser, a sociologist at Goldsmiths College, has noted that PDAC members were outspoken in their faith in the validity of quantified, statistical data, over anecdotal patient reports, in deciding “whether the phenomenon we have heard about today is a real one” (FDA 1991, quoted in Fraser 2005: 9). This trust in the validity of clinical trial data over patient reports has been a recurrent theme throughout the now decades-long inquiry into the safety of SSRIs. Despite patient

reports of adverse effects starting to number in the hundreds of thousands across the UK and North America, regulators in both Britain and the United States have lent credence to those reports only when the appearance of clinical trial data has made it impossible to ignore them any longer.

Following the publication of studies from Teicher and Beasely, dozens of studies have investigated the question of whether SSRIs induce suicidality or homicidality. One of the most cited studies from the 1990s is from Susan Jick and colleagues at Boston University (Jick 1995), who investigated the UK's database of primary care physicians to examine physician reports involving 170,000 patients who had been prescribed antidepressants from among three main classes of antidepressants: tricyclics, MAOIs, and SSRIs. Though the authors found evidence that patients on fluoxetine were almost twice as likely to commit suicide as patients on other antidepressants, they attributed the difference to selection bias (which is the term for when, for example, patients at a greater risk of suicide are given a drug which is thought to be safer in overdose), and not to something inherently more problematic with the fluoxetine (Jick 1995; Breggin 2003/2004).

By the end of the 1990s, debates over SSRIs were no closer to resolution than when Teicher's study in 1990 first initiated speculation over the safety of the drugs. Over the years, dozens of studies and opinion reviews have arisen, with evidence that both dispelled suggestions of a link to suicidality or acts of deliberate self-harm on the one hand (for example Kahn, Warner et al. 2000; Markowitz 2001; Nutt 2003; Gibbons 2005; Licinio and Wong 2005), and which support the idea of a link on the other (Healy 1994; Donovan, Kelleher et al. 1999; Donovan, Clayton et al. 2000; Healy 2000; Fergusson, Doucette et al. 2005; Whittington, Kendall et al. 2005).

In the late 1990s, David Healy, who had become interested in the SSRI debates in part through serving as an expert witness on a number of high-profile litigations in the United States, conducted a randomized double-blind study comparing the effects of sertraline (Zoloft), with a non-SSRI antidepressant (reboxetine) in healthy volunteers. He found that many of the 20 individuals taking part developed adverse mental effects while on sertraline, and two became severely disturbed (Healy 2000). Healy's study is criticized, however, for the small number of its participants, and thus for having little statistical significance – a weakness repeatedly returned to by the informants I spoke with during interviews.

Shortly following the publication of his sertraline study, Healy was offered a job as clinical director of the Centre for Addiction and Mental Health (CAMH) at the University of Toronto – one of the most well-reputed centres for the study of mental health in the world. During a lecture at the University of Toronto a few months in advance of taking up his post, Healy publicized his views on the potential dangers of Prozac. Shortly after his lecture, CAMH, which is heavily funded by Prozac's manufacturer Eli Lilly, withdrew its job offer. In a letter seeking to explain why Healy's offer was rescinded, David Goldbloom, then Physician-in-Chief at CAMH, made it clear that Healy's "scientifically irresponsible" remarks and his divergence from the "published scientific literature" had led the questioning of his credibility and appropriateness for the post of CAMH's clinical director (Goldbloom 2001).

Your presentation on November 30th raised further questions within our staff and faculty regarding your suitability for this particular position. No one disputed your academic freedom to say whatever you want in our or any other university or in academic health sciences centre. However, the extremity of the views that you espoused caused an extraordinary stir among the people who would be your junior and senior colleagues within CAMH and the University Department of Psychiatry. I am referring to your seemingly casual statements of people killing themselves on and because of fluoxetine, of antipsychotics essentially causing more harm than good, and of increasing hospitalization in the modern era. These people felt your remarks were scientifically irresponsible, incompatible with published scientific evidence and hence

incompatible with the mantle of responsibility of leadership of a clinical and academic program (Goldbloom 2001).

In the years since Healy's offer was withdrawn, a number of news articles have reported that Eli Lilly has suppressed evidence from clinical trials where patients suffered adverse reactions to fluoxetine (Elias 2006), something that has cast doubt on the scientific reliability of previously published studies. These news reports, as well as a recent admission from GlaxoSmithKline that some of the clinical trials they carried out for paroxetine (which goes under the trade name Seroxat in the UK; Paxil in US) indicated a six-fold suicidal risk over placebo (Lenzer 2006), have validated Healy's criticism of Eli Lilly and GSK when the majority of medical opinion sided against him.

Healy's position was further supported by the appearance of a leaked company document suggesting GSK withheld clinical trial data where more children exhibited adverse effects while on paroxetine than on placebo. The document, dated October 1998 and entitled, "Seroxat/Paxil Adolescent Depression – Position Piece on the phase III clinical studies" was first described in an article in the *Canadian Medical Association Journal* (Kondro 2004: see also Figure 2, where a copy of the GSK memo is provided), and is now widely available on the Internet. It stipulates that company representatives should be cautious in disseminating the results of Study 329 and 377, two trials carried out in adolescent populations in the mid-1990s in a range of countries, stressing that "it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine" (excerpt from GSK 2007, downloaded from the Alliance for Human Research Protection). Noting the need "to effectively manage the

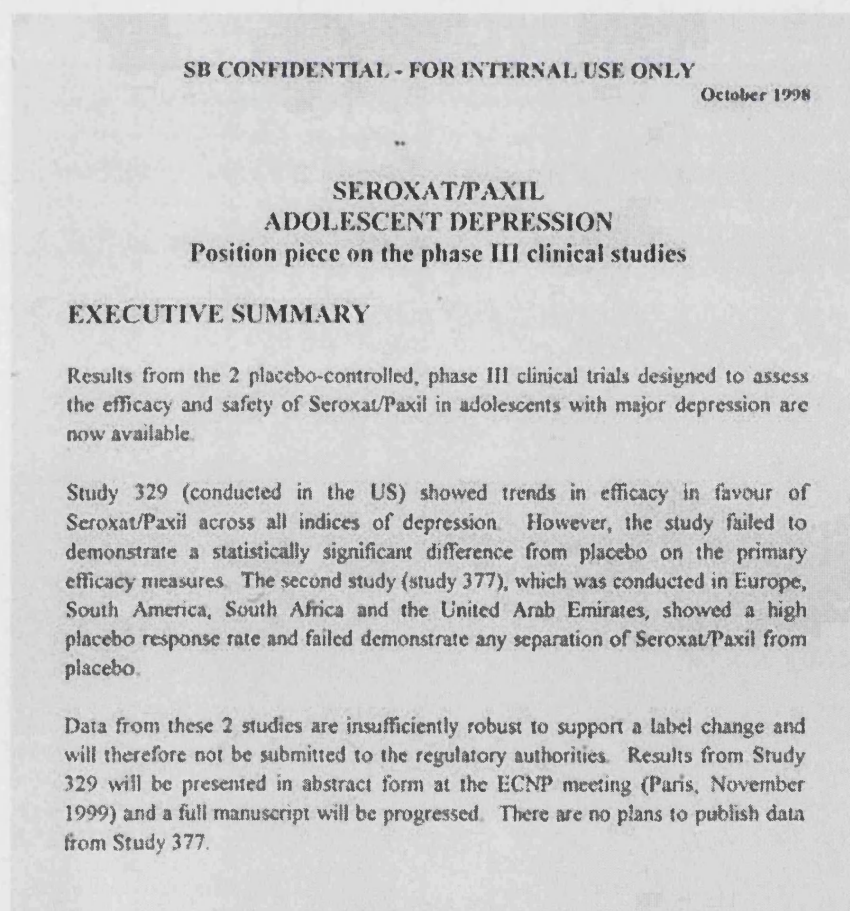
dissemination of these data in order to minimize any potential negative commercial impact," the document states:

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures...*Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities* (excerpt from GSK 2007; see Figure 2, emphasis added).

Two years following the dissemination of this internal memo, the results of Study 329 were published in the *Journal of American Child Adolescent Psychiatry* in 2001 with the conclusion "Paxil [Seroxat] is generally well tolerated and effective for major depression in adolescents" (Keller 2001).

Figure 2: GSK position piece on Phase III Clinical Studies

(Source: Alliance for Human Research Protection
<http://www.ahrp.org/risks/SSRI0204/GSKpaxil/index.php>)



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SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies
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SITUATION

2 SB sponsored, placebo-controlled, phase III clinical trials have been conducted, Study 329 (US) and Study 377 (Europe, South America, South Africa and Saudi Arabia), in order to assess the efficacy and safety of Seroxat/Paxil (up to 40mg/day) in the treatment of adolescents (aged between 13 and 18 years and 11 months) with unipolar major depressive disorder (diagnosed according to DSM IIIR, Study 329 or DSM IV criteria, Study 377).

Study 329 was a placebo-controlled, imipramine comparator study with an 8 week acute treatment phase followed by a 6 month extension phase. The acute phase has completed and the extension phase is due to complete at the end of 1998. 275 patients were recruited to the study. Results from the acute phase of this study show that there were no statistically significant differences from placebo on either of the primary efficacy parameters (change from baseline in HAMD total scores and the proportion of responders-where response was defined as a $\geq 50\%$ reduction from baseline in HAMD score or a HAMD score ≤ 8 at endpoint). However, trends in favour of paroxetine compared with placebo were seen across all the indices of depression (change from baseline in HAMD total [$p=0.133$], HAMD responders [$p=0.112$], CGI [$p=0.094$] and K-SADS [$p=0.065$] scores) and statistically significant differences from placebo were observed in the proportion of patients in remission (defined as a HAMD score of ≤ 8 at endpoint). In general, the response to imipramine was similar to that for placebo. The 6 month extension phase has now completed and is scheduled to report at the end of 1998.

Study 377 was a 12 week placebo-controlled study, conducted in 276 adolescents with major depression. There was a high placebo response rate in this study and no statistically or clinically significant differences from placebo were observed on either of the primary efficacy variables (proportion of patients achieving a $\geq 50\%$ reduction from baseline in total MADRS scores and change from baseline in the K-SADS-L depressive subscale score). The only differences from placebo (secondary efficacy variables) were seen in a subgroup of patients who were ≥ 16 years of age.

Possible explanations for the high placebo response include;

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- 1) The large number of study visits
- 2) the duration of the assessments
- 3) The fact that concomitant psychotherapy was not excluded
- 4) Question marks about the adequacy of using currently available diagnostic criteria and rating scales in younger patients
- 5) Adolescents may be more susceptible to a placebo effect
- 6) Developmental issues. Children and adolescents may respond in a pharmacologically different manner due to quantitative and/or qualitative differences in neurotransmitter/receptor systems.

Conclusions from these studies:

- There were no differences in the safety profile of Seroxat/Paxil in adolescents when compared to that already established in the adult population
- The efficacy data from the above clinical trials are insufficiently robust to support a regulatory submission and label change for this patient population.

OTHER DATA:

Ongoing studies: SB France are conducting a locally funded double-blind, comparative study of Seroxat/Paxil with clomipramine in adolescents with major depression (Study 511). In addition, a study in adolescents with OCD (Study 453) is underway in the US. This study comprises a 16 week open label Seroxat/Paxil treatment phase, followed by double-blind, randomisation to paroxetine or placebo for a further 16 weeks of treatment. The regulatory acceptability of these 2 studies needs to be established.

Published data: A review of the literature shows that 2 studies assessing the use of paroxetine in the treatment of 34 adolescents and children with depression have been published (Rey-Sanchez and Gutierrez-Cesares, 1997, Findling et al, 1996).

The first study (Rey-Sanchez and Gutierrez-Cesares, 1997) was a retrospective survey of data from 25 adolescents (aged 13-17 years) treated with paroxetine. Patients were diagnosed according to ICD 10 criteria. In 13 of the patients unipolar major depression was not the primary diagnosis. 17 patients received paroxetine as a monotherapy, 8 also received concomitant psychotropic medications (n=7 benzodiazepines, n=1 haloperidol). Paroxetine was administered at doses of 10mg (14 patients) or 20mg/day (11 patients). No specific depression rating scales were used, response was based on clinical judgement. 76% patients

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had a satisfactory response (11 complete remission, 8 improved with residual symptoms). A lack of satisfactory response in was observed in 6 (24%) patients. Eight patients reported side effects (somnolence or sleep disorders n=6, asthenia n=4, nausea n=3, tachycardia n=2, diarrhea n=2, headache n=2, orthostatic hypotension n=1, restlessness n=1). Two patients were withdrawn due to one due to anxiety, one due to hypotension and dizziness)

The second study (Findling et al; 1996) was conducted in 9 patients aged between 7-15 years (children and adolescents) meeting DSM IV criteria for a major depressive disorder. Symptomatology was assessed using HAM-D for subjects aged 13 to 15 years, and the childhood depression rating scale (CDRS) subjects aged 12 or younger. Paroxetine was initially given at a dose of 10mg/day. This was escalated to 20mg/day if the patient had not responded after 4 weeks of treatment. 8/9 patients responded to treatment with paroxetine. Three patients had complete remission, 5 patients had a >50% reduction in total CDRS score from baseline. CGI improved in all patients. One patient withdrew from the study at week 2 due to an adverse experience. This patient was found to have elevated serum paroxetine levels and was a poor 2D6 metaboliser. Assessment of pharmacokinetic parameters in this study showed that paroxetine had a similar half life to that reported in the adult population (15.7h [sd 9.0h] vs 24h, respectively).

COMPETITOR ACTIVITIES:

Lilly are believed to be in near to completing their phase III clinical trials in adolescent depression. One relatively large placebo-controlled 8 week study with an open 12 month follow-up period conducted in 96 patients (aged 8-18 years) has recently been published (Emslie et al; 1997 and 1998). These data show that 56% (27/48) patients on fluoxetine (20mg/day) compared with 33% (16/48) patients on placebo were rated as much or very much improved on the CGI at Week 6 (p=0.02). In the 12 month follow-up period, 85% (n=74) patients recovered from the depressive episode (47 on fluoxetine, 22 on placebo and 5 on other antidepressants or lithium). Twenty nine (39%) of the patients (36% of those who had recovered on fluoxetine (17/47) and 41% of those who had recovered on placebo [9/22] had a recurrence of depression during the 12 month follow-up (a higher recurrence rate than seen in adults). Other published data on fluoxetine are from small open studies or individual case reports (Colle et al; 1994).

Pfizer already have positive data (including PK data) and are licenced in the US for the treatment of adolescent OCD. In addition, Pfizer are also believed to be conducting clinical trials in adolescent depression. Available published data are

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limited, derived from small open studies in adolescent depression (McConville et al, 1996; Tierney et al; 1995)

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

PROPOSALS

- Based on the current data from Studies 377 and 329, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements relating to adolescent depression at this time. However data (especially safety data) from these studies may be included in any future regulatory submissions, provided that we are able to go on and generate robust, approvable efficacy data. The rationale for not attempting to obtain a safety statement at this time is as follows;
 - i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use
 - ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.
- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.
- The regulatory acceptability of Studies 511 and 453 and any other data in this patient population will continue to be investigated.

GSK's handling of Studies 329 and 377 led to legal actions in the UK, where the MHRA launched a criminal investigation in 2003 to ascertain whether GSK had withheld information on the drug's effect, and in the US, where the New York Attorney General Eliot Spitzer launched a lawsuit in August, 2004 accusing GSK of consumer fraud by depriving consumers and doctors of information necessary to make informed decisions (Lancet 2004). GSK later settled out-of-court with Spitzer, refusing an admission of wrongdoing, but agreeing to pay a fine of \$2.5 million. Four and a half years after the MHRA launched its criminal investigation into GSK, the inquiry is still ongoing. I examine the inquiry in greater detail in Chapter Seven.

Until suggestions surfaced of deception on the part of manufacturers, Healy has been generally spurned among medical circles for continuing to stress his views on SSRIs, even undergoing brief investigation by the General Medical Council (GMC), as the result of a letter from David Nutt, who, as mentioned earlier, has taken an opposite perspective to Healy on the safety of SSRIs. On January 26, 2006, Nutt sent a letter of complaint to the GMC suggesting the council should be concerned about the ethics of Healy's conduct during his 1999 clinical trial comparing reboxetine with sertraline. The GMC initiated an investigation that was later dismissed (GMC 2006).

During my interviews with practitioners, I found the rigour of Healy's data was repeatedly questioned because of the outspokenness of his views. It seems that Healy transgressed what Porter has identified as one of the cardinal rules of science – the golden rule of impersonality. At root here is a key paradox. Commercial research has the obvious bias of being motivated by the need to earn profits for shareholders. Yet, despite this fundamental interest underlying corporate research, the data from large-scale commercial clinical trials conducted by companies such as Eli Lilly and GSK is routinely valued by regulators as being more credible than smaller observational studies conducted by lone practitioners such as David Healy. In practice, as is revealed by reports from regulatory hearings such as the PDAC inquiry in the United States and the MHRA's inquiry into SSRIs in the UK, large-scale commercial studies are considered more 'objective' than small-scale studies conducted by personally invested researchers. The moral authority of numbers lends corporate research its questionable status of impartiality.

The role of strategic ignorance at the MHRA

Between 2002 and 2004, BBC's Panorama programme ran three documentaries that suggested that, in contrast to prevalent medical literature on the safety of SSRIs, tens of thousands of individuals in the UK had suffered adverse reactions to the drugs. The programmes focused in particular on complaints surrounding Seroxat, which was considered by a number of people interviewed during the series as the most problematic of the class of drugs. Over four million people tuned into Panorama's first programme in the series, *Secrets of Seroxat*. The programme attracted a phenomenal response, with the BBC receiving about 65,000 phone calls, 124,000 web hits, and 1,374 emails (Medawar and Hardon 2004). Shortly following the programme, the MHRA directed its Committee on Safety of Medicine (CSM), a working group mandated to advise the MHRA on all drug licensing, to address the question of SSRI safety.

The convening of the CSM following the Panorama programme in 2002 was not the first time the MHRA had addressed the questions of SSRIs and suicidality. Following the publication of Teicher's study in 1990, the CSM had first reviewed the issue, finding no evidence of a causal link. Between 1998-2000, there was a UK exercise to harmonise safety information for SSRIs, which led the CSM to advise that all summary of product characteristics (SPC) labels on SSRIs should reflect general clinical experience that suicidal behaviour could increase in the early stages of treatment. In 2001, the CSM again considered data relating to suicidal behaviour and concluded that there was no evidence to confirm a causal association between SSRIs and suicidal behaviour (MHRA 2004).

Following the first two Panorama programmes, the MHRA chose to address the issue again, calling a meeting of the CSM in March, 2003. A series of news article leading up to the March meeting revealed, however, that half of the members

of the initial CSM working group directed to assess the safety of SSRIs held a number of shares in companies such as GlaxoSmithKline. The MHRA moved to dissolve its first working group entirely and set up a new one composed of practitioners who had fewer ties to industry (Boseley 2003).

A few months later, the newly formed group was handed a confidential dossier from GlaxoSmithKline that contained surprising evidence: Two of the company's own clinical trials indicated Seroxat contributed to suicidal thoughts in children and adolescents. When the group received the dossier from GSK, they alerted the MHRA of the finding, spurring the regulator to issue an immediate contraindication of the use of Seroxat in children.⁷

In December 2003, the MHRA expanded the contraindication to include all SSRIs except Prozac. A year later, in December 2004, the regulator advised the National Institute of Clinical Excellence (NICE) to revise its clinical guidelines for the use of antidepressants in the treatment of depression across all age groups. The actions taken by British regulators helped to spur 2004 FDA hearings on the safety of SSRIs. As a result, in October 2004, the FDA directed SSRI manufacturers to add a "black box" indicated the increased risk of suicidal thoughts and behaviour in children and adolescents being treated with SSRIs (FDA 2004).

These actions by the FDA and the MHRA remain contested, with manufacturers and some health professionals suggesting the decision to enforce black box warnings has led to increasing suicide rates, because fewer children and adolescents are being treated with SSRIs (Vedantam 2007). Conversely, a number of

⁷ The question of why GSK handed the SSRI working group this dossier remains unresolved. Some of my informants, such as Kendall and Brook, who sat on the SSRI working group, thought that GSK was seeking a licence extension for the use of Seroxat in a paediatric population, and had misgauged the regulators' reaction to the data. GSK, on the other hand, has argued it sought to bring the evidence of increased risk to the regulator's attention (GSK 2007b).

observers suggest the MHRA and FDA have been negligent for not acting more quickly when evidence of the lack of safety of SSRIs in children first arose (Lenzer 2004; Healy 2006). Some also argue, as I explore below, that the MHRA failed to act quickly when evidence arose of the lack of efficacy of SSRIs across all age groups in doses higher than 20 milligrams.

As noted earlier, the MHRA chose to reconfigure its 2003 SSRI working group after the media pointed out the group's links to the pharmaceutical industry. A second response of the MHRA to public concerns over the composition of its SSRI expert working group was the decision to include, for the first time in MHRA history, a member of the public among the scientific experts asked to assess the safety of the drugs. Richard Brook, then chief executive of the mental health charity Mind, was asked to serve as that non-scientific member.

I spoke with Brook in February, 2005. Brook has had a volatile relationship with the drugs regulator. After serving on the group for a year, he resigned in protest over what he called a cover-up by the agency of the finding that daily doses of SSRIs over 20mg were no more effective at treating depression, regardless of severity, than doses at 20mg or less. The SSRI working group discovered this through a re-analysis of clinical trial data that had been in the possession of the MHRA for over ten years, overlooked during four previous inquiries into the safety of the drugs. Though the finding had a bearing on the 17,000 individuals in Britain who were receiving daily doses of SSRIs at 30, 40 or 60 milligrams – increasing their risk of suffering adverse effects – the working group chose not to publicly disclose the new information. When Brook voiced his dissatisfaction over the decision to withhold the information, MHRA CEO Kent Woods sent him a letter indicating he would be in breach of the Medicines Act should he reveal the data, and noting he had advised Brook's lawyer

of this fact (see Figure 3). Brook chose to raise the issue with the then Health Minister, Lord Warner, who intervened in Brook's favour, directing the regulator to publish the findings over dosing levels (Boseley 2004).

As discussed in the previous chapter, the government's 1911 Official Secrets Act and Section 118 of the 1968 Medicines Act prevent MHRA regulators, as well as any expert advisors on committees such as the SSRI working group, from publicly divulging any commercial information related to the licensing applications for medicines. If they do so, they face serving jail terms of up to two years (MHRA 2006). During my interview with Brook, I asked him to what extent expert advisors serving on MHRA working groups were reminded of the commercial confidence laws stipulated in 1968 Medicines Act, and the need to avoid public disclosures of findings adverse to industry:

LM: I'm curious how strongly they stress that to you.

RB: At every meeting, the chairman reads the riot act over the meeting reminding you if you say anything then you're going to be in trouble. Every set of minutes has a confidentiality clause on it at the beginning saying these papers are confidential. The whole organization, at the time that I was involved with it, was geared up to a sort of secrecy – and very, very scared of any details coming out in terms of the pharmaceutical [industry], scared of the effect the pharmaceutical companies will take if the information is leaked... I don't think the secrecy is driven by a desire to – they claim it's about not scaring people – but ultimately, from my observations, I'd say it was always predominantly driven by their fear of having a row with pharmaceutical companies over leaking commercial secrets.

Figure 3: MHRA Letter to Richard Brook

(Source: MHRA)

Mr Richard Brook
Chief Executive
Mind
The Mental Health Charity
15-19 Broadway
London E15 4BQ

020 7084 2100
020 7084 2548
kent.woods@mhra.gsi.gov.uk

8th March 2004

Dear Mr Brook

I am responding to your letter dated 2nd March 2004 about the publication of data on the dosage of Seroxat (paroxetine), which you also copied to Lord Warner and Sir Alasdair Breckenridge. Lord Warner will be writing to you separately.

You asked for permission to make public information concerning the dose response of Seroxat, and advising me of your intention to put the information in the public domain on Tuesday 9th March or shortly afterwards.

I would remind you that as a member of the Expert Working Group you undertook to respect the confidentiality of all information which you received as a result of that membership. The work of such advisory groups, and the participation of external members in them, would be undermined if this duty of confidence were to be ignored. You should also be aware that the release of confidential information under these circumstances would constitute an offence under Section 118 of the Medicines Act 1968.

There must also be concern that any precipitate release of such information would lead patients to stop or sharply reduce their Seroxat treatment, exposing them to a real risk of withdrawal reactions and/or clinical relapse.

The MHRA and I therefore cannot agree to your request for permission to put into the public domain the material relating to Seroxat and I ask you not to publish or to disclose it.

I am copying this letter to Anthony Collins, Solicitors, who I have been informed act for you and Mind.

Yours sincerely

Professor Kent Woods
Chief Executive

cc. Anthony Collins Solicitors

Dir:off1st04richardbrook199204

The excerpt from Brook, as well as the letter from Woods, help to illustrate why the drugs regulator, despite having information about the adverse effects of SSRIs for over a decade, did not immediately disclose the information to the public. As discussed earlier, I suggest that a two-fold anti-strategy, stemming from the regulator's funding structure and the need to retain public trust, works against such disclosures in practice.

The most valid criticism of my argument is that suppressing evidence of a drug's effects would likely generate *more* public outcry than disclosing such evidence and risking public mistrust of the agency's possible negligence in licensing the drug to begin with. Particularly given the increased application of the precautionary principle, where regulators are expected to take protective regulatory measures even where reliable scientific evidence of causes is lacking, in European drug licensing and in European regulation in general (cf. Majone 2002), it seems only logically that the MHRA would strive to disclose adverse effects as soon as they learned of them – for fear of public recrimination if they did not.

As logical as this seems, it is apparent – as the example of Brook indicates – that not only were members of the MHRA reluctant to act swiftly on evidence of the inefficacy of SSRIs at doses above 20 milligrams, it was suggested prosecution might befall those who did. Historically, there have been a number of precedents to the MHRA's hesitation in this case. Abraham, for example, has written of the case of Halcion, a triazolobenzodiazepine manufactured by Upjohn and first licensed in Britain in 1978. Although the UK's Committee on Safety of Medicines first investigated reports of significant adverse effects in 1978, it took over a decade of inquiries – and significant media attention – before Halcion was banned in the UK in 1993. Abraham, who noted that the British regulatory authorities' "non-detection of

Upjohn's handling of Halcion permitted patients to be exposed to an unsafe drug for nearly 13 years," stressed an additional factor which might have hindered the UK regulator's ability to swiftly remove the drug – that is the extensive appeals system open to manufacturers if the regulator bans a drug:

In the UK, the problems regulators may face after suspending a drug product, may be compounded by the elaborate professional appeals procedures open to manufacturers before a case may even go to court. Under these circumstances, regulators are also confronted with the possibility that the professional credibility of the medicines licensing system might be damaged if the various appeals bodies contradict the suspension or revocation decision by the regulator (Abraham 2002: 1687, 1686).

Abraham's point supports the argument that, against the logic of the precautionary principle, there are a number of constraints that hinder the UK regulator from acting quickly on the removal of a drug suspected of carrying significant risks to patients.

In my interview with Woods, he disagreed with Brook's suggestion that he had threatened with prosecution by the MHRA. He also raised a point relevant to suggestions of secrecy at the MHRA, which is the question of the current status of Section 118, purported in the media and in sociological analyses to have been repealed as a result of the 2005 enactment of the Freedom of Information Act (e.g. Abraham 2007):

KW: [Brook] asked me a question: would I give him my permission [to release data]. And I said no. And I said there were three reasons why the answer was no. And to mention, in doing so, that he was going to be in breach of Section 118 was not exactly a threat of prosecution. We didn't have policeman standing outside his door. When I saw that matter presented by Mr. Brook in the media as though we had threatened him with a prosecution I thought that was a complete misstatement. He had asked for permission to break an undertaking of confidentiality, and I had declined that permission. And I had explained why. That was not a threat of prosecution. In fact, nobody has ever been prosecuted under Section 118. It is something that was brought into the Medicines Act, and it progressively became an impediment to transparency. In fact, it has been amended since then.

LM: I saw the amendment...in some ways, it could be said to have strengthened Section 118. In that it made individuals who had left the

MHRA beholden to not release data after they left. So in some ways, would you argue that Section 118 was strengthened?

KW: Well, we had our lawyers look into this. And the intention was to modify Section 118 in the opposite direction, to allow us to become more transparent as an organization. And specifically to allow us to put into the public domain the evidence base on which our advice was given.

LM: Definitely. It feels like they didn't actually give that authority.⁸

JK: Well, I leave it to the lawyers to concern themselves with the precise wording of amendments to old legislation. But the reason it was done, and the effect of the amendment subsequently, was to allow us – for instance, as we did with paediatric SSRI trials – to put the data out in the public domain.

LM: Yes. Given your legal situation that was commendable. And I know individuals who feel that you made a calculated and courageous gamble to put those SSRI trials on the website.

KW: Yes.

LM: They felt that the MHRA individuals who had done so were protected by the idea of the public uproar if a company tried to go after you.

KW: Absolutely.

Woods may feel that sending a letter indicating Brook would be in breach of the Medicines Act if he disclosed information about dosing levels, and adding that he had taken the liberty of advising Brook's lawyer of that fact, was not a threat of prosecution. Brook, however, saw it differently, and I have tended to agree. A second point of interest in the excerpt is the suggestion that the MHRA took a legal gamble in releasing the SSRI trials that it eventually did. The fact that such disclosure was an anomaly in the MHRA's history suggests a history of institutional barriers towards public openness.

I have suggested above that the heuristic of anti-strategy helps to explain multiple and contradictory pressures on a regulatory or bureaucratic structure that

⁸ My question here is based on an email from Anne Thyer, of the MHRA's policy division, who wrote the following to me in April 2006: "Section 118 was not repealed in January 2005. It was instead amended (I attach the relevant entry) to restrict disclosure of information to those persons who are, or were acting on behalf of a person who is, a public authority for the purposes of the Freedom of Information Act 2000. This is therefore aimed at preventing, for example, former Agency staff or consultants disclosing information/documents that they retained after working for the Agency" (MHRA 2006).

can work to contravene its explicit aims. This leaves unanswered, however, the question of how a regulator manages to function at all within the confines of multiple, conflicting pressures. Here is where the value of both strategic ignorance and strategic uncertainty begins to emerge. Ignorance and uncertainty, wielded as tools, helps to provide a solution to the need to both serve the public and to conceal things from its sight.

The analysis of ignorance within social theory

It has only been fairly recently that social theory has turned to the question of the strategic use of ignorance, both within bureaucracies and beyond. Arguably the most comprehensive treatment of the phrase “will to ignorance” stems from Nehamas’ analysis of Nietzsche. Nehamas argues, for example, that Nietzsche saw knowledge not as the opposite of ignorance, but as its “refinement,” something Nietzsche stressed in order to cement his central claim that the most seeming of antitheses – truth and error, knowledge and ignorance, good and evil – were not opposed to each other, but complementary, deriving their character and their meaning from their interrelation (Nehamas 1985: 44-46). Apart from Nehamas’ analysis, there has been almost a complete absence of attention to Nietzsche’s use of the phrase “will to ignorance” (one exception is Landy 2002).

The social and political usefulness of ignorance in general has received slightly more attention from social theorists. Drawing on Elias Canetti’s identification of secrecy as the very core of power, Michael Taussig has written on the political value of ignorance, and the way that often the most important social knowledge is “knowing what not to know” (Taussig 1999: 9). This “negativity of knowing,” he suggests, lies so intrinsically at the heart of a vast range of social powers and

knowledge that “we fall silent when faced with such a massive sociological phenomenon, aghast at such complicities and ours with it, for without such shared secrets any and all social institutions – workplace, marketplace, state and family – would founder” (Taussig: 7). Scholars such as Paul Gilroy (2006) and Robert Proctor have called for the need to pay more attention to the social and scientific uses of ignorance:

Historians and philosophers of science have tended to treat ignorance as an ever-expanding vacuum into which knowledge is sucked – or even, as Johannes Kepler once put it, as the mother who must die for science to be born. Ignorance, though, is more complex than this. It has a distinct and changing political geography that is often an excellent indicator of the politics of knowledge. We need a political *agnotology* to complement our political epistemologies (Proctor 1996: 8).

In his essay *The ecology of ignorance*, Niklas Luhmann offers one of the most penetrating observations of the political and social functions of ignorance, particularly through his observation of how the purposeful cultivation of ignorance helps to facilitate the defence of nonliability for one’s actions. When one admits no understanding, one is not pressured to assume any blame: “The communication of ignorance relieves authority. Whoever communicates knowledge absorbs uncertainty and must consequently take responsibility for the truth and untruth of his knowledge. Whoever communicates ignorance is excused” (Luhmann 1998: 91).

The anthropologist Paul Rabinow notes that Luhmann’s work on ignorance helps to illuminate a key limitation of the modern conception of the ethics of responsibility. In short, Luhmann reminds that the ethical imperative to take full responsible for one’s actions is difficult given that the contingency of both the present and future renders it impossible to gauge the full effects of one’s decisions. The more appropriate tactic, Rabinow stresses, should not be the (impossible) effort to fill every gap in our ignorance, but to recognize that one’s existence in an ecology

of both partial and permanent ignorance is unavoidable. He suggests that accepting the limitations of one's knowledge would help to deflate the authority of those making pronouncements which present the future as inevitable and therefore unchallengeable. Embracing the reality of ignorance becomes a defence against the oppressive certainty of others (Rabinow 2004).

As noted earlier, among the most comprehensive analyses of ignorance has been work by Smithson, who notes that scientists have found the following uses for ignorance:

- 1) Consciously acknowledged and constructed ignorance is a prerequisite to learning or discovery and, therefore, to much scientific research.
- 2) Tolerance of ignorance facilitates a climate of creativity and entrepreneurship.
- 3) Vagueness or ambiguity may be used to avoid being wrong, to enhance generalizability, or to attain consensus.
- 4) Strategic admission of ignorance can enhance one's reputation for scientific cautiousness or sobriety.
- 5) One may gain a competitive advantage from the ignorance of colleagues.
- 6) Appeals to ignorance may be used as justification for maintaining the status quo or halting some potentially harmful activity.
- 7) Appeals to ignorance may also assist in lessening accountability for one's decisions or actions (Smithson 1993: 134).

Analyses such as these have helped to illuminate the strategic use of ignorance. But they are few. In short, social theory has either been slow to apprehend the strength of strategic ignorance, or else it has confused the emergence of ignorance with a breakdown in rationality and not, as I am suggesting of it, that it is indicative of a rational strategy itself.

For an understanding of the chimerical character of ignorance, for the way it transcends easy binaries such as truth / untruth, rationality / irrationality, one perhaps has most success looking outside of social theory to literature. Particularly in Kafka's *The Trial*, where Josef K. struggles to defend his innocence to a quasi-mythical

battery of faceless jurors and impassive judges during a legal trial of dubious origins, one starts to approximate the half-rational / half-irrational strength of ignorance which our social theorists, trained for a long tradition in the strict separation of rationality and irrationality, have often misperceived. Anti-heroes from literature such as Josef K., or Orwell's Winston Smith, labouring away at the Ministry of Truth where statistics are adjusted daily to suit the demands of politics, help serve as a reminder to pay attention to the consequences of the unplanned and the unapparent. They remind of the imperative, whenever approaching proceedings such as the MHRA's perennial inquiries into SSRIs, to search not for what was found, but for what has, often through necessity, been obscured.

They also point, through the admitted dissimilarities between Kafka's Josef K. and Orwell's Winston Smith, to a valid criticism of the heuristic of ignorance as I have used it. As it stands it is too broad. For example, is the suppression of evidence deliberate, as appears the case in the threatened prosecution of Brook? Or, as it seems with the misreading of the clinical trials in the MHRA's possession, simply an unintended and unconscious consequence of organizational procedures? If the concept of strategic ignorance is to have any analytical purchase, it must be both elaborated and nuanced a great deal more. Below, I sketch some initial suggestions for its elaboration.

Toward a typology of strategic ignorance

Building on the analyses of ignorance above, I suggest that the case of the SSRIs illuminates the following political uses of ignorance: liminal, factual, and defensive. Below, I examine each of these in turn.

Liminal ignorance: the public dissemination of non-knowledge

Liminal ignorance is the presentation – whether deliberate, or unconsciously adopted as a result of tacit, organizational pressures – of a public front of ambiguous half-knowledges; chimerical knowledges which precariously straddle the boundaries between public and private information. This form of ignorance is often visible in the cleansing of the seemingly superfluous aspects of process that are deemed irrelevant for inclusion in a given inquiry's final report.

In the MHRA's recent report, for example, the treatment of Richard Brook – the lay member of the SSRI working group who was threatened with prosecution for seeking to publicize safety data – makes no appearance among the report's findings. Instead, the inclusion of non-medical, lay members is praised in a salutary manner, as in this passage from the working group's chair, Professor Ian Weller: "The crucial role of the lay members of the Group has also set a precedent which now the MHRA are taking forward in other ways" (MHRA 2004: ix). It is not mentioned that the decision to include more than one lay member stemmed from Brook's resignation, forcing the need to locate another non-specialist member in the first place. The removal of Brook from the process of deliberating over the safety of SSRIs serves as an illustrative example of the political usefulness of strategic ignorance. Brook was privy to the same knowledge as the other members of the MHRA's SSRI working group. His mistake was in wishing to publicize that information, in threatening to disturb the careful veneer of non-knowledge which the group was seeking to maintain publicly. He was penalized for breaking the rule of ignorance.⁹

⁹ I am grateful to Scott Vrecko for helping me expand on this point.

Factual ignorance: the political usefulness of conditionality

Factual ignorance emerges when the complexity and contradictions inherent in competing scientific facts are employed as a form of political capital. This point draws on an insight raised by Luhmann in *The ecology of ignorance*. In the essay, Luhmann argues a cultural and political shift has taken place in recent decades. In recent times, those carrying political or cultural power have increasingly grasped that uncertainty provides a reprieve from having to answer for the consequences of one's knowledge. At times, uncertainty is a more advantageous tool than certainty: one need not provide answers for what one could not have known.

Drawing on Luhmann's insight, I argue that a "politics of conditionality" has recently emerged, where regulators, politicians and scientific experts are increasingly aware of the rhetorical authority of appearing conditional about a course of action. Luhmann reminds of the need, whenever scrutinizing a regulatory or governmental document, to attune oneself to the political capital inherent in appearing uncertain rather than authoritative about a given topic. With this in mind, one observes how often the MHRA findings are presented in a tentative, inconclusive and qualified manner, particularly on the question of suicidality in adults. The working group notes, for example, that among adult users of SSRIs, "a modest increase in the risk of suicidal thoughts and self-harm for SSRIs compared with placebo cannot be ruled out." Despite the indication of some adverse effects, the report concludes that the evidence of a relationship between SSRIs and suicidality is not robust enough to warrant regulatory action. Throughout the report, statements are often written in an equally conditional rather than an authoritative manner:

The conclusions of the Group and the evidence on which they are based are set out in the report. Inevitably, they represent a snap shot in time, based on the

evidence available to the Group during the course of its work (MHRA 2004: iv).

Compare the tentativeness of the statement above to the excerpt earlier from Luhmann: “Whoever communicates knowledge absorbs uncertainty and must consequently take responsibility for the truth and untruth of his knowledge. Whoever communicates ignorance is excused.” Ambiguity, in other words, offers protection from blame.¹⁰ It is the conditionality of statements such as the one above that helps to safeguard a body such as the MHRA from legal culpability when allegations of outright deception surface from the companies they are mandated to regulate. This leads to a third aspect of ignorance.

Defensive ignorance: non-knowledge = non-liability

Defensive ignorance – where silence on the part of a regulator can be attributed not to purposeful secrecy, but simply to errors or difficulties in the interpretation of conflicting facts – is exonerating. It offers a sort of institutional alibi when evidence emerges of fraud or malfeasance among the bodies that a regulator is meant to police. The purposeful suppression of data is often criminal. Mere oversight or human fallibility less so.

¹⁰ Power, in *The Audit Explosion*, quotes usefully from Bourdieu on the strategic value of ambiguity: “Any practice must have ‘enough logic for the needs of practical behaviour, neither too much – since a certain vagueness is often indispensable, especially in negotiations – nor too little, since life would then become impossible’, Pierre Bourdieu, ‘From Rules to Strategies’, in *Other Words: Essays towards a Reflexive Sociology* translated by Matthew Adamson, Polity Press, Cambridge 1990, p.73. Quoted in Power 1994: 54.

To offer an example of this: as reported in the *British Medical Journal*, GlaxoSmithKline admitted in 2006 that clinical trial evidence in its possession for over a decade indicated patients prescribed Seroxat were six times more likely to attempt suicide than those given a placebo:

GlaxoSmithKline announced last week that they had found an increase in suicidal behaviour in adults taking paroxetine (Paxil / Seroxat) compared with Placebo...The Glaxo study confirms the suggested link between suicidal behaviour and antidepressants in adults (Lenzer 2006).

Following this disclosure from GlaxoSmithKline, attention once again turned to the MHRA's non-detection of such evidence during its previous half-dozen inquiries into the safety of SSRIs. Bewilderment was voiced yet again at the MHRA's failure to detect the adverse effects earlier. As one critic noted:

It is difficult to understand why the MHRA failed to notice the most troubling evidence of a 6-fold increased suicide risk in the adult trials as well as the increased risk of hostile, aggressive (homicidal) behaviour...it appears that drug safety regulators on both sides of the Atlantic have either participated as partners in fraud or they have demonstrated utter incompetence in reviewing the data that documents the risk of suicide in clinical trials. (AHRP 2006).

The problem with this and other criticisms of the MHRA is that, like Josef K's futile efforts to elicit rational explanations from his persecutors, such critics refuse to revise their assumptions of how a regulator *should* act. They search for a logic and functionality in the wrong places. They assume a regulator would seek to act on its explicit goals, and in this case either ban or change the warning labels on drugs shown to carry serious adverse effects. Such critics fail to ask after the regulator's interest in not acting according to its explicit aims. They do not ask after the value of *not* acknowledging information contrary to tacit organizational demands. "It is difficult to understand why the MHRA *failed to notice* the most troubling evidence of a 6-fold increased suicide risk in the adult trials," notes the statement above (my

emphasis). In fact, this is easy to understand. Strategic ignorance on the part of the regulator was a rational consequence of the need to adhere to the various anti-strategies which acted as antitheses to the goal of protecting patient safety.

Conclusions

In this chapter, I have made four key arguments. Firstly, I have suggested that the controversy over SSRIs illustrates the professional repercussions when individual practitioners choose to publicize their private concerns over commercial influences on medicine. I argued, drawing on the example of Healy, that there exists a burden on practitioners to remain politically neutral and to adhere to the status quo of dominant opinion or thought, lest they lose the approval of their peers.

Secondly, I have argued that Power's insights on auditing are relevant to drugs regulation in the UK. Power has stressed that audits are remarkably impervious to their own failure, and that in the rare instance when attention does occasionally turn to the question of process, either individuals, or the specifics of individual audits, are blamed instead of the system of auditing itself. The same is true of drugs regulation. Though the MHRA carried out no fewer than a half-dozen inquiries into the safety of SSRIs, clinical trial data in the regulator's possession failed to reach the public until a seeming aberration – Richard Brook's refusal to adhere to protocol – forced the issue into the media.

Throughout the controversy over SSRIs, the solution to debates has not been to intensify scrutiny of the system through which drugs are regulated, but to ask the drugs regulator to conduct yet another inquiry. In this way, through mandating the MHRA to again address the issue, the authority of the regulator is strengthened rather than challenged. When one reverses this general tendency, and peers beyond

isolated cases of failed inquiries to the process of regulation itself, one discerns that a number of structural barriers, such as the MHRA's funding structure and its need to maintain public reputation, hinder it from carrying out the outspoken aim of arbitrating on the safety of drugs. This observation is not restricted to the MHRA. In the next two chapters, I examine more obstacles, such as the relationship between the MHRA and governmental bodies such as the National Institute for Health and Clinical Excellence, that have made it hard to reach conclusions on the safety of SSRIs.

Thirdly, I have explored the role of ignorance as a strategic resource within regulatory and bureaucratic structures in order to address the question of why the MHRA failed in inquiry after inquiry to produce the answers for which it was ostensibly looking. Through attention to anti-strategies and the value of ignorance, one realizes that in failing – in *not* managing to reach conclusions on the safety SSRIs – the MHRA has been able to maintain its relationship with industry.

Finally, through the discussion of GSK's admission that its own RCT data revealed more suicidal risk, and the questions that raises over the MHRA's earlier interpretations of GSK's trial data, I have alluded to the focus of the next chapter: The history and role of RCTs in evidence-based medicine, and ethical and political concerns with their use.

Chapter 5: Regulatory battles at NICE and the MHRA

Introduction

Building on previous analyses of RCTs (Ashcroft 1997; Adams 2002; Corrigan 2002; Corrigan 2002; Dehue 2002; Petryna 2005; Lakoff 2007; Petryna 2007; Will 2007), in this and the following chapter I develop a theoretical framework for understanding the political implications of RCTs. To do so, I draw on the work of Jack Goody (1977), Bruno Latour (1986), Maurice Bloch (1998) and Nikolas Rose (1999) on the political uses of literacy and numeracy. I apply that framework to a case study of the debates over SSRIs and the efforts of people such as Kendall and Shooter to develop a better understanding of the safety of the drugs from published and unpublished trial data.

In the first half of this chapter, I explore the development of the RCT, from its origin in agricultural and human experimentation in the early 20th-century, to post-WWII efforts to apply the technology to medicine, to more recent debates over the ethical and political questions posed by RCT design and use. In the second half, I return to the SSRI controversy in order to examine the efforts of practitioners to elicit RCT data from government regulators in the UK.

History and methodology of randomized controlled trials

The double-blind randomized controlled trial – where neither the clinical investigator nor the patient is aware who has received the treatment and who the control – is widely considered the most rigorous and scientific way to determine the clinical efficacy of a new medicine or therapy. Three distinct elements of the double-

blind RCT – the use of randomization in order to reduce statistical chance, the use of control groups to help manage the influence of confounding variables, and the use of blinding to reduce the influence of both patients and practitioners – contribute to the status of RCTs as the most rigorous method for determining a treatment's benefit.

The adoption within medical experimentation of each of these elements – randomization, controlling for confounders, and blinding – has a long history, characterized by much interdisciplinary exchange across fields such as statistics, biology, epidemiology and psychology.

Surprisingly, given the status of RCTs within medicine today, sociologists and historians of medicine and science have only recently begun to chart their historical development. One of the most cited analyses is Harry Marks' *The Progress of Experiment: Science and Therapeutic Reform in the United States: 1900-1990* (1997). In an unpublished PhD dissertation, *The Making of the Clinical Trial in Britain, 1910-1945: Expertise, the State and the Public*, Desiree Cox-Maksimov offers a similar history in Britain. Marcia Lynn Meldrum's PhD dissertation *Departures from Design: The Randomized Clinical Trial in Historical Context, 1946-1970* (1994) offers a social history of the RCT's development.

Traditionally, it has been practitioners and scientists themselves, rather than sociologists or historians of medicine, who have paid the greatest attention to the development, use and methodology of RCTs (see, for example, Littlefield 1982; Armitage 1995; Rees 1997; Kaptchuk 1998; Kaptchuk 1998; Healy 2001; Chalmers, Hedges et al. 2002; Vandenbroucke 2002; Doll 2003).

Drawing on the analyses above, the next section explores how the three factors historically viewed as merits of the RCT – the use of blinding, control groups and random allocation – have come to be seen as politically contentious by those opening

the “black box” of RCTs in order to assess the methodology’s valued status in medicine today.

Managing subjective and objective bias: the role of randomization and control groups

The British statistician and geneticist Ronald Fisher is credited with introducing ideas of randomization to statistical experimentation, as the result of a series of agricultural experiments which he conducted in the effort to determine the superiority of types of grain. Fisher’s involvement with experimentation began in 1919, when he was appointed as a statistician to an agricultural experiment station in Rothamsted. While there, Fisher observed the problem of confounding variables on crop outcomes. He asked the question: if two grains of rice planted in different fields produced a 10% difference in yields, how was one to determine whether it had been the inherent superiority of the grain, or differences in soil, temperature and moisture, that contributed to the greater yield?

To address this, Fisher proposed that the experimental plots of land be divided into narrow strips, and the grains assigned to a given strip by the use of a chance mechanism. By subdividing a single field, the number of observations from a single experiment increased, and the effects of variation in soil or temperature on experimental error were minimized, thus enabling statistical inferences to be drawn from the results. Fisher’s vital contribution was his insistence on the use of a chance mechanism to assign treatments, helping to insure the validity of inferences drawn. Though it took decades for the idea to persuade sceptics (both among statisticians themselves, and among the medical clinicians asked to apply principles of

randomization in their clinical practice),¹¹ Fisher's ideas had a large influence on statistical theory, helping to reshape a range of disciplines from medicine, to genetics, psychology and economics (Hacking 1990; Gigerenzer 1995; Marks 1997: 141-142).

The initial reluctance of British and American clinicians to embrace statistical tools such as random allocation extended towards the introduction of a separate mainstay of scientific experimentation: the use of control groups. The introduction of controls to medical experimentation is generally attributed to James Lind's test of lemons for the prevention of scurvy in the British Navy in the 1740s. Though Lind's ideas were vital to the development of the field of epidemiology, and continue to exert a popular influence on advocates of RCTs today (see, for example, Chalmers, Hedges et al. 2002), it took more than a century for his writing to have any serious effect on medical experimentation. As the historian Ted Kaptchuk notes, by the beginning of the 20th-century, clinical researchers had only just begun to understand the importance of concurrent controls in trials. One difficulty was the fact that, "an obvious no-treatment arm became a recruitment and retention nightmare. Patients would demand "real" treatment or seek out cointerventions" (Kaptchuk 1998: 423). These early concerns over the appropriateness of withholding treatment have been rejuvenated in recent years in discussions of the ethics of placebo use, randomization, and informed consent within RCTs.

Lind's early work "staging" controlled experiments among sailors, as well as early controlled trials such as the Michigan tuberculosis trial of 1926-31, were

¹¹ As well as sketching a "prehistory" of the pre-20th-century use of randomizers before Fisher's groundbreaking *The Design of Experiments* (1935), Hacking provides an account of the initial reception of Fisher's ideas in *Telepathy: Origins of Randomization in Experimental Design* (1988). Hacking notes that when Fischer asked a research student to write a dissertation on randomized experimental design, no one was willing to examine it – such was the initial reception of Fisher's ideas.

gradually complemented by the work of American sociologists and psychologists who began to compose artificial research populations, examining human behaviour in controlled and staged settings, in order to try and manage, in the words of one early investigator, the “disturbing incomparability of social groups [which] would always plague experimentation with humans” (quoted in Dehue 2002: 82). For early 20th-century social scientists such as educational psychologist William McCall, forming comparable research groups and constructing artificial research environments was a way of managing what some researchers saw as the “confounding” variables of race, social status, family structure and gender on human behaviour (see for example Oakley 1998).¹²

The privileging of artificial settings as an avenue toward deriving more objective insights into human behaviour, and the influence of that privileging on the development of controlled trials, is something that a number of social scientists flag today as a key problem within the methodology of RCTs. Historian of psychology Trudy Dehue has argued that:

[O]nly if the importance – or even reality – of inter-individual relations is denied, does it make sense to investigate people in artificial groups disconnected from their familiar school-classes, colleagues, friends, enemies, and (in artificial settings) their familiar things. Only on the assumption that historically and culturally established relationships do not matter can the RCT be a rational research strategy (Dehue 2002: 84).

¹² McCall himself might reject the way that the very techniques he helped develop in psychology have led to the suggestion, among some proponents of controlled trials, that the evidence derived from RCTs is more objective, and therefore more credible, than the evidence derived from uncontrolled experiments. In a book review published in 1937, McCall notes that, “[the authors] commit the conventional error of many scientists, who confuse the objective and the quantitative, and overstress the objective and abuse the subjective, thus contributing further to the unhappy conflict between science and philosophy (pp. 13-14). Science should recognize that the objective is no more than the consensus of the subjective; that science itself is as deeply concerned with value or feeling as is philosophy; and that there are times when, even to science, the subjective is preferable to the objective” (1937: 67-68)

Dehue's comment points to one of the key criticisms levelled at RCTs today, which is that the results of a staged experiment, regardless of the size of the study and the sophistication of its design, can rarely be replicated among clinical populations, where cultural, economical and familial variables influence the effectiveness of treatments. This suggestion – of an irreducible disconnect between a medicine's performance during experimental settings and its everyday use – has long been voiced by practicing clinicians reluctant to incorporate the findings and evidence from RCTs to their daily treatment choices. If some clinicians remain opposed to RCTs today, there was even more resistance during the early-20th-century, before individual experiments such as Bradford Hill's trials with streptomycin in the 1940s began to convince clinicians of the relevance and usefulness of controlled trials for the practice of medicine.

Marks notes that it was in large part the writings and the work of Bradford Hill, in particular his 1948 study of streptomycin's efficacy in the treatment of tuberculosis, that helped to convince both US and British clinicians of the relevance of statistical analyses for clinical practice. In *The Progress of Experiment*, Marks suggests a sophisticated distinction between the perspectives of Fisher and Hill on the merits of randomization within trials. He argues that for Fisher, the chief virtue of randomization was its role in helping to minimize *objective* bias (it helped a researcher to identify how significant the external role of chance had been in determining the experiment's outcome). Hill, on the other hand, thought that the main value of randomization lay in its ability to help moderate the hope and expectations of investigating researchers; its key virtue was helping to manage *subjective* bias. As Hill notes, the use of random allocation ensured "that neither our personal idiosyncrasies, consciously or unconsciously applied, nor our lack of

judgement have entered in to the construction of the two (or more) treatment groups and thus biased them in any way” (Hill, quoted in Marks 1997: 145).

Marks develops his distinction between Fisher’s focus on the management of objective bias, and Hill’s focus on subjective bias (which Marks describes as the “two epistemological claims [which] underwrite the randomized clinical trial”), in an article focused on Fisher’s belief in the democratizing virtues of randomization, probability and inference (Marks 2003). Fisher, Marks argues, was passionately attached to the view that randomization helped any “thinking man” to grasp the intricacies of statistical theory, protecting the “right of other free minds” to come to their own conclusions about a given debate or phenomena (Marks 2003: 933-934).

Fisher’s views seem echoed by those today who suggest that evidence-based medicine is a democratizing element in health, creating more avenues for patients and practitioners to contest more hierarchical, paternal forms of medicine based on the eminence and status of individual medical authorities. In the next chapter, I suggest the hopes of Fisher have not come to pass: the availability of RCTs has not, in contrast to the views of many advocates of EBM, rendered it more feasible for practitioners or patients to contest authoritative assessments of a treatment’s harm or efficacy, unless they have access to RCT data which can support their objections.

Masking certainty: the role of blinding

The early preoccupation with minimizing the personal biases of trial investigators led researchers to adopt blinding mechanisms which helped to mask the certainty and knowledge of both practitioner and patient. The purposeful use of uncertainty in RCTs in order to wrestle certainty from their results is one of the most epistemologically interesting – and ethically fraught – aspects of the methodology.

Which makes, as Katchuk has pointed out, the relative lack of attention to the history of blinding in controlled trials all the more interesting.

In the essay “Intentional Ignorance: A history of blind assessment and placebo controls in medicine,” Kaptchuk launches a polemic against (the few) previous descriptions of the use of blinding in randomized controlled trials. Although blind assessment, he argues, is considered today to be a fundamental component of modern medical research, attention to its practice and development has been “nil to minimal, occupying at most a few short paragraphs in a relatively few articles and books.”

This dearth leads him to assert that:

The history of masked assessment seems veiled in obscurity, with the implication that this method was not available until well into the 20th-century, when an eternal transhistorical scientific verity somehow became obvious to researchers. The aura of objectivity and neutrality attached to blind assessment itself may have benefited from this absence of a past (1998: 390).

Tracing the development of blinding in early attempts to root out quackery and fraudulent claims among 18th-century mesmerists and 19th-century hypnotists, Kaptchuk asserts that the novelty of blinding in 20th-century controlled trials was its root in the relatively recent idea that even the most respected biomedical researchers were capable of distorting trial outcomes if their personal biases were left unrestrained:

Previously, the taint and accusations of bias, prejudice, overenthusiasm, credulity, and delusion were reserved for deviant healers; now, what was once a fringe threat was internalized. Even the judgements of the most senior clinicians concerning the efficacy of new therapeutics were suspect. “Bias” now haunted medicine (1998: 430).

Kaptchuk notes that the merits of the blinding were espoused on two levels: the practical and the epistemological. Practically, blinding enabled randomization to function properly (if an investigator was aware which patient was receiving a dummy

or control pill, the treatments could not be said to have been truly randomly allocated). Epistemologically and politically, the process of blinding helped investigators meet a number of newly established requirements, such as the need to demonstrate to regulators that a trial had been conducted according to sound, scientific methodological principles. The well-controlled, double-blind RCT soon became the epitome of both scientifically and *morally* incontestable experimentation. As Kaptchuk notes, “the adoption of blind assessment in medicine has had as much to do with shifting political, moral and rhetorical agendas and technical research design issues as with scientific standards of evidence. [Blinding] has been a vehicle to confer social authority and moral legitimacy” (1998: 432).

What should not be underappreciated in the above statement is the discussion of the need to justify one’s research design to external sources. The legitimacy of the RCT as *the* standard for investigation in medicine grew in tandem with two separate, but related phenomena. Firstly, efforts to regulate the growing pharmaceutical industry through the establishment of bodies such as the Food and Drug Administration in the United States, and the Medicines Control Agency (the MHRA’s predecessor) in the UK. Secondly, increasing attention to the problem of medical ethics, and the duty, first enshrined in the Nuremberg Code in 1946, to offer legal protection to the human subjects of medical experimentation.

It is perhaps of little surprise that the randomized controlled trial – widely seen as a harbinger of neutral, objective, scientific evidence – came to be relied on as both a means to determine which novel pharmaceuticals were sufficiently efficacious and safe to be awarded licences, and as a way to manage human experimentation in controlled, institutional settings that were subject to regulatory oversight and scrutiny by government bodies. Since 1970, the FDA has required drug manufacturers to

obtain evidence of the safety of new drugs through undertaking “adequate and well-controlled trials,” which ideally incorporate control groups assigned at random, and which are large enough to permit quantitative evaluation of treatment effects using “appropriate statistical methods” (Marks 1997: 130). In the UK, drug firms are generally required to submit at least two randomized controlled trials demonstrating efficacy and safety in order to have a new product licensed. Since the 1960s, there has emerged, across Britain, North America and Europe, a panoply of Research Ethics Committees (in the UK) and Institutional Review Boards (in the US) which oversee the administration of trials according to national and international guidelines.

In an interview conducted by David Healy with Linford Rees on the latter’s pioneering introduction of clinical trials to the field of psychopharmacology, Rees described the emergence, during the 1950s and 1960s, of this new onus to prove to regulators not only that the evidence derived from a clinical trial demonstrated the therapeutic value of a new indication, but that the trial itself had been conducted according to standard, methodological principles such as randomization and blinding:

Healy: Obviously when the first compounds were introduced, this didn’t happen through double-blind methods. When do you think the industry got the message that they should be doing them?

Linford Rees: Oh, I think after the initial trials of chlorpromazine, iproniazid, imipramine and so on. They realized that in order to get through the Committee for the Safety of Drugs and later the Safety of Medicines Committee – I was on both committees – results of double-blind controls trials became obligatory (Rees 1997: 11).

In the interview, Rees also raises an issue that has emerged in recent years (more than a half-century after Rees himself first flagged it) as one of the more politically contentious issues surrounding clinical trial dissemination: the publication of negative trial results.

Healy: Where did you get your interest in double-blind placebo controlled trials?

Linford Rees: Well, looking back, Ralph Picken, the Professor of Preventative Medicine in Cardiff, taught us the pitfalls of uncontrolled trials. He was talking about controlled trials in hygiene and in treatment, when I was a student, and I think that's where the seed was sown...I think the very first one I did was a study on the substance betasyamine in the treatment of anxiety. There were theoretical reasons why this could be helpful in depression or anxiety. So I organized a double-blind study but the results were totally negative. I think we should have published that, but people were reluctant to submit negative results. It's important to publish negative result but a lot of people don't want to waste time.

Despite such early concerns, the publication of negative trials results has not been widely raised as either an ethical or a political issue until very recently, when it was first aired by proponents of the evidence-based medicine movement such as Chalmers, who began, after systematic efforts to synthesize published evidence, to flag the problem of the retention of negative trial results by both academic and industry researchers (see, for example, Chalmers 2006). Such efforts, however, as this thesis demonstrates, have failed to affect a culture where there is no legal onus to publish treatments that are shown to be inefficacious or unsafe.

Despite the fact that RCTs are now viewed, by regulators and by the majority of clinicians working in Europe and North America, as the gold standard methodological tool for determining a drug's safety and efficacy, their role in medicine remains a contentious one. In the next section, I provide an outline of the ethics and politics of the methodology and use of RCTs – themes which are further developed in Chapter Six.

“Gentlemen don't do them: Ethical and political concerns surrounding randomized controlled trials

The primary ethical issue raised by RCTs is the question of the need, enshrined in international legal statutes first established by the Nuremburg Code in 1947, and

further strengthened by the Declaration of Helsinki in 1964, to protect the human subjects of medical experimentation from harm or exploitation. The goals of the Nuremburg Code and the Declaration of Helsinki in 1964 were bolstered by the publication of a seminal essay by the anaesthesiologist Henry Beecher, *Ethics and Clinical Research* (Beecher 1966). This essay, in which Beecher argued that a number of unethical experiments were routinely conducted in medicine, has had a lasting impact on the establishment of the field of bioethics in the United States, Britain and more widely.¹³

Because RCTs often differ from clinical conditions in their purpose, methods and justification of patient risk, they raise a number of specific ethical problems. As Miller and Silverman have pointed out, “procedures foreign to medical care are routine in RCTs – randomization, masked assignment of treatment, protocol-defined restrictions on treatment, placebo controls, and clinically unnecessary procedures and tests implemented to measure study outcomes” (Miller and Silverman 2004: 362). Two of the main ethical concerns centre on the use of placebos in trials, where seriously ill individuals are potentially denied access to the most proven therapeutic for their condition if randomly allocated to the placebo arm, and secondly on questions of informed consent, and whether patients are adequately informed of risks and benefits prior to participation in trials.

The history of the regulation and governance of placebo controls in trials has been a controversial one, with vehement advocates on either side of the question of whether placebo use is justifiable. Opponents argue that placebos are always unethical if a proven treatment is available, while proponents argue that placebo use

¹³ There is an extensive literature on the development of research codes to govern human experimentation. For some studies which provide a general overview, focused on the regulation of RCTs in psychiatry, see Carpenter et al 2003, and Shamoo and Irving 1993.

is acceptable on a case-by-case basis, providing patients are not at risk of serious harm and have given consent (see Miller 2000; Miller and Brody 2002). National and international regulatory standards differ widely in their guidance on placebo controls, and the regulation of trials in general. The Declaration of Helsinki stipulates that every patient enrolled in a medical study must be assured of receiving the best proven diagnostic and therapeutic methods, a stipulation that has long been read as prohibiting the use of placebos. Recently, partly as a result of lobbying by bodies such as the European Medicine Evaluation Agency, a 2002 clarification to the Declaration has lessened the stringency of its amendment on placebo use, stressing that clinical trials with placebo controls are occasionally acceptable as long as the condition being studied is “minor” and the safety risks negligible (Carpenter, Appelbaum et al. 2003).

The effect of codes such as the Declaration of Helsinki has been geographically and nationally variable. For example, though neither US and nor British laws explicitly require compliance with the Declaration, its underlying principles, such as the prohibition against placebo use except in rare cases, have been influential with Institutional Review Boards and Research Ethic Committees which arbitrate on the ethical acceptability of a trial application, and have often looked more favourably on applications where the use of placebo is not proposed (Carpenter, Appelbaum et al. 2003).

Partly in order to circumvent ethical constraints against placebo use in countries such as the UK and the US, there has been a large increase in clinical trials which are conducted in developing regions where ethics codes are often less stringently enforced – a topic that has recently drawn much sociological and anthropological attention (Nguyen 2005; Petryna 2005; Petryna 2007). In a working

paper entitled *Drug Development and the Ethics of the Globalized Clinical Trial*, Petryna argues that it has recently become routine for multinational, pharmaceutical companies to “scan the world, statistically and innovatively carving out new populations for larger and more complicated trials to assess the drug safety and efficacy demanded by US regulators and consumers.” She notes this phenomenon has, on the one hand, been condemned by human rights advocates who argue that codes such as the Declaration of Helsinki should be universally upheld, and, on the other hand, has been defended by some public health activists who suggest that it is a case of “ethical imperialism” to insist that regions facing massive health crisis should be forced to implement Western codes of conduct at the expense of new medicines reaching local populations (Petryna 2005: 3).

The issue of the outsourcing of trials to developing regions is perhaps the most obviously political of the questions concerning the design and use of RCTs. Other political questions have centered on gender issues, and the privileging of male over female subjects in phase II studies (Corrigan 2002; Corrigan 2002); economic issues, and the question of whether the poor in both developed and developing regions are unduly exploited as research subjects (Nguyen 2005), and, as was mentioned earlier, questions of disclosure and the retention of negative trial results by both academic and industry researchers for economic or professional gain (Chalmers 2006).

The ethical and political issues above point to the most explicit questions raised by RCTs. Recently, however, it has been suggested that a host of methodological factors within the internal design of RCTs should be viewed as ethical and political questions in themselves (Ashcroft 1997; Healy 2001; Lakoff 2007). For example, things such as patient inclusion criteria, where patients most likely to demonstrate a certain outcome are purposefully recruited for trials (Lakoff 2007), and the recording

of treatment outcomes by trial investigators – both of which I explore further in the next chapter – have an effect on a trial’s ‘objectivity,’ in the sense of being free of the influence of confounders. Yet, despite the recognition that social processes are central to an RCT’s production, its final evidentiary conclusions are often viewed – by regulators and by clinicians – as being more safeguarded from the influence of external biases than the evidence which is derived from individual, clinical encounters.

For a number of years, people have questioned the implication – institutionalized in regulatory licensing requirements – that the evidence derived from RCTs should be viewed as scientifically superior to the anecdotal evidence of a treatment’s risks or benefits derived from clinical observations or patient reports. Observers suggest that because RCTs, like all forms of scientific practice and experimentation, are partly produced by a configuration of social relations, it is the very claim itself that they produce more objective knowledge that should be questioned (Dehue 1997; Dehue 2002).

By pointing out, however that RCTs are embedded in a set of political and social relations that have an influence on their findings, key questions are left unasked. For example, what moral and political demands are met by the privileging of RCTs as a more objective form of reasoning? Why, even among practitioners who doubt the objectivity of the evidence derived from individual RCTs, do RCTs in general retain their “gold standard” status? Why is the moral legitimacy awarded to RCTs so intractable?

A possible reason for the lack of attention to such questions might lie in the false sense of novelty attached to the questions that *have* been asked the most vocally. A tendency in much of both the sociological and the scientific literature on

RCTs has been to assume ethical and political questions have been raised only recently. In particular, many observers attribute the emergence of such questions to the 1960s and the years following the publication of the Declaration of Helsinki and Beecher's influential essay. But, as observers such as Richard Doll and Peter Armitage have argued, ethical issues were at the forefront of some of the earliest experiments using randomized, controlled methodologies.

Bradford Hill, for example, was preoccupied by the implications of randomization and placebo use, and the ethical problems raised by withholding medicines from terminal patients on the control arms of trials. Doll suggests that Hill drew on utilitarian justifications of the need to accrue the greatest possible benefit to as many as possible in order to resolve his own concerns. The RCT, in Hill's views, was a means to visually demonstrate to regulatory bodies the efficacy of a new treatment in order to help secure funds for its more universal provision:

Overriding all this evidence in favour of the drug was the fact that at that time exceedingly little of it was available in Great Britain, nor were dollars available for any wide-scale purchase of it from the USA. Except for that situation it would certainly on ethical grounds have been impossible to withhold the drug from desperate ill patients. With that situation, however, it would, the Committee believed, have been unethical not to have seized the opportunity to design a strictly controlled trial which could speedily and effectively reveal the value of the treatment (Hill, quoted in Doll 2003: 930).

This central tension – between the effort to balance the needs of current patients with the desire to develop better therapies for future ones – has remained at the heart of discussions of the practical benefits of RCTs.

Marks has pointed out a related issue, suggesting that historians puzzling over “the relative absence of ethical discussions over medical research in the first twenty years after World War II” have in part “been looking in the wrong place.” In fact, proponents of RCTs were outspoken in attaching ethical virtue to RCTs, asserting

that RCTs would help in countering the misleading, advertorial claims of therapeutic efficacy advanced by the pharmaceutical industry (Marks 1995: 157). By helping to generate scientific evidence – accessible, visible, and demonstrable to both clinician and patient – the RCT helped to provide an ethical defence against arbitrary, unscientific claims of a treatment's worth. The physician who refused to implement the evidence from a controlled trial was not simply acting parochially or archaically: she was acting *immorally* – unduly exposing patients to the unsubstantiated claims of industry, or worse, to the vagaries of her own personal whims. In recent years, despite the fact that majority of RCTs are either conducted or funded by the pharmaceutical industry, the methodology itself seems to have retained its early status as a defence against industry.

There have been some exceptions to the early perception of RCTs as representing a scientific integrity divorced from industry influence. Cochrane, hailed by many as the leading founder of the evidence-based medicine movement, described such an exception during an interview in the 1980s:

the use of randomised clinical trials has increased. The only tragedy is that it hasn't spread throughout the world. Very few are done in France and Germany and none in Russia and it's really confined to Canada, the United States, Scandanavia and United Kingdom. If all the countries would join in we could get the answers far more rapidly. The attitude of the Germans is quite extraordinary. I was over there only about three years ago and my German was still very good and I gave a standard lecture on the use of the randomised controlled trial in organising the treatment of heart disease. A very straight forward thing: the randomised controlled trials of place of treatment, length of stay, and all that sort of thing, and I've never had a more riotous reception. My god they were rude to me, in German. Fortunately I can fight back in German and we had a real battle. They considered me utterly unethical and I complained that they were unethical: they weren't checking that they were giving their patients the best treatment. And it went on for nearly three quarters of an hour. I got pretty tried. The real story comes at the end. The professor, took me out and gave me dinner and on the way out in excellent English said, " you know, Dr. Cochrane, you don't seem to understand about controlled trials. Controlled trials are done by the pharmaceutical industry. Gentlemen don't do them (Cochrane 1987: 14, quoted in Wahlberg and McGoey 2007)

Fifteen years later, it appears Cochrane's view has eclipsed that of the senior

professor. The dream of conducting more randomized clinical trials throughout the globe, and developing large, accessible syntheses of their results, has been realized. Cochrane's aims have been crystallized within the global phenomenon of evidence-based medicine. And yet the professor's early admonition against the influence of industry still haunts, particularly as recent controversies over drugs such as Vioxx and this SSRIs have suggested companies often distort or purposefully misinterpret clinical trials results.

My main aim in this section has been to introduce the key tool in efforts to determine the safety of SSRI antidepressants: the randomized controlled trial. Since its origins in crop experimentation, the RCT has served as two forms of defence for clinicians and regulators: firstly, as providing an *ethical defence* (however merely symbolical) against the claims of industry. Secondly, as providing a *moral defence* for practitioners who wish to a) justify their treatment decisions to patients and peers, and b) even more crucially, legitimate the decision to deviate from standard treatment procedures.

In the next section, I argue the development of RCTs as the leading standard for determining medical efficacy has fostered the unexpected consequence of limiting decision-making to the sphere of statistical evidence – regardless of the social and political relations which produced the evidence in the first place. In order to convince others that a drug carries previously undetected risks, as Healy suggested of the SSRIs, a practitioner *must* have recourse to RCT evidence which validates his or her position. Dissent from dominant opinion, therefore, is limited to those who have the scientific capital to support their views through drawing on contrary RCTs. The growth of scientific experimentation in medicine – once hailed by Fisher as something which would democratize debates over treatments, allowing any “thinking

man” to scrutinize evidence and reach his own conclusions – has had the opposite effect: it has helped to narrow the boundaries of medical debates to those who have the means and expertise to produce and access RCT evidence.

To put this in conceptual terms, it is within the nature, as Bourdieu has illuminated (1999), of a dominant authority to influence and prescribe even the forms of resistance which that authority has engendered in the first place. I call this tendency “methodological mimesis,” and its effect in medicine has been clear: those who doubt the evidence from a particular RCT must defend their objection through recourse to a competing study. Thus, through the constant, cyclical recourse to the adjudicating authority of RCTs – even by antagonists battled over the relative worth of individual studies – the faith in RCTs as superior arbiters on the safety and worth of a treatment is perpetually reinforced.

Accessing the data on SSRIs: Informational battles between the MHRA and NICE

In the lecture series *Society Must Be Defended*, Foucault describes the following goal: To ask whether the metaphor and schema of war could serve as the conceptual basis for an analysis of power relations in peaceful societies. He answers affirmatively, arguing that “power relations, as they function in a society like ours, are essentially anchored in a relationship of force that was established in and through war” (Foucault 1997: 15). This insight leads him to invert Clausewitz’s aphorism that “war is a mere continuation of policy by other means,” and to suggest conversely that it is policy itself, in the modern societies where extreme civil violence is lacking, which emerges as a continuation of war by other appearances. The metaphor of war enables Foucault to apply concepts such as “tactics”, “strategy” and “relations of force” to the regimes which point to the absence of civil violence as indicative of the

peaceful and tranquil relationships within their jurisdiction, and which purport to defend those jurisdictions through protecting them from the vicissitudes of external wars. Through the metaphor of struggle, Foucault is able to interrogate the seeming binary relationship of peace and war, and expose the ways that power relations within civil societies are often predicated on motifs of subjugation, domination and rebellion.

The specific discourse of war which Foucault identifies as underlying peace exists in “silent, larval forms,” beneath the “visible brutality of bodies and passions” which characterize palpable, visible warfare (1997: 268, 269). It is a discourse, he stresses, which inverts the traditional values of intelligibility, and which exploits understandings of knowledge, truth and ignorance as key resources. One of the preferred choices of ammunition in the civil battles which Foucault seeks to unveil is knowledge itself, and the effort to establish a right to knowledge that “is stamped with dissymmetry” (1997: 268).

Foucault’s perception of war as the essential underlying metaphor for peace has elicited much criticism by observers who suggest his perspective affiliates him with the very scholars, such as Hobbes, whose insights he deems problematic in *Society Must Be Defended* and in other work. Marshall Sahlins, for example, argues in the essay *The Sadness of Sweetness* that Foucault accepts without adequate scrutiny the dubious notion of humans as innately, naturally antagonistic (Sahlins 2000). Even sympathetic followers of Foucault note there is some discrepancy between Foucault’s earlier proposition in *Society Must be Defended* of an almost binary opposition between those with power and those without, and his later work on governmentality where he stresses the dispersed, multi-faceted nature of power (see for example Fontana and Bertani 1997).

Although such criticisms have some merit, the remainder of this chapter takes as an underlying premise the aptness of Foucault's insight of war as a cipher of civility. The goal of such a premise is to apply the key tropes of war – tropes such as strategy, tactics, negotiation, casualties and others – to the analysis of efforts by patients and practitioners to obtain information from the MHRA on the safety of SSRIs. Through the metaphor of war, it is possible to both describe the different strategic relations employed by patient groups and practitioners as they forged novel alliances in the efforts to elicit information from the MHRA, as well as to illustrate the depth of anger and bitterness many practitioners voiced during interviews over what they viewed as the MHRA's unforthcoming attitude to the release of clinical trial data.

Time and again, practitioners such as Tim Kendall, Michael Shooter and Susan Bailey returned to their concerns over the MHRA's handling of the SSRI controversy, voicing bewilderment at the lack of transparency at the MHRA. Their bewilderment stemmed in part from confusion over the explicit aims of the regulator. Given the onus on physicians and regulators to protect the safety of patients, they assumed the MHRA would collaborate on efforts to reach clarity on the safety of the antidepressants. Their assumption was dispelled. Gradually, it became evident that if a complicity existed, it existed between producers and their regulators, not consumers. The heuristic of struggle and battle is intended to help contextualize the strategic tactics which were employed once the illusion of shared interest was lost.

"It's their job to be tough": Regulatory and policy conflicts between the MHRA and NICE

In the previous chapter, I argued that an anomalous event, contrary to typical procedures at the MHRA – Richard Brook's refusal to stay silent regarding the

efficacy of SSRIs at doses over 20mg – drew attention to the possibility of systemic dysfunction surrounding the MHRA's many inquiries into SSRIs. In the spring of 2003, it was a similar accident – the chance glimpse of a confidential company memo – that alerted a group of UK psychiatrists and psychologists to problems surrounding the safety of SSRI use in children. The circumstances surrounding this incident point to a number of communication problems between the MHRA and NICE.

As noted earlier, the recent emergence of EBM in the UK and other countries has led to the development of institutions which produce evidence-based guidelines which clinicians are directed to use in their clinical practice. NICE is the main body in England and Wales responsible for producing such guidelines. Though NICE is ostensibly promoted, on its website and by its advocates, as a body which is independent of government, there exists some government interaction and oversight, particularly as the NHS is legally bound to provide funding and resources in England and Wales for medicines and treatments which are recommended in NICE's technology appraisal guidelines. According to the NICE website, all doctors, nurses and healthcare practitioners working within the NHS are expected to follow NICE guidance on a given treatment. If they do not follow NICE guidance, patients are asked to register a formal complaint (NICE 2006). Thus there exists, in theory, a close degree of coordination between NICE, which produces national treatment guidelines, and the MHRA, which is legally responsible for the licensing and post-market surveillance of all medicines and medical devices in Britain.

In order to create national guidelines, NICE commissions policy recommendations from specialists in, say, cardiology or mental health care. In 2003, NICE asked the National Collaborating Centre for Mental Health (NCCMH) to

produce recommendations for the treatment of depression in children and adolescents. The NCCHM staff in charge of the project, Tim Kendall and Craig Whittington, set about their task by writing to various drug companies, requesting all unpublished and published clinical trials testing the safety and efficacy of SSRIs in children. As he describes:

TK: When we did the [NICE] childhood depression guideline – in fact, whenever we do any guideline – we wrote to all the stakeholders, including the pharmaceutical companies, saying, “Do you have any additional data and in particular any unpublished trials?” At that point in time, the answer was a unanimous “No, there is no additional data.”

LM: They said, No, we’ve got no data,” or “No, we won’t give it to you?”

TK: They said, “No, we haven’t got any.” That was early on. Although, one drug company referred us to the MHRA to see the drug company’s own trials! Now, while we were doing this particular guideline, we were contacted by the MHRA because they were undertaking a review of SSRIs in children. I think this was initiated by a Panorama programme some 18 months before, which had raised the issue that SSRIs might increase self-harm in children who are depressed. MHRA reviews are effectively secret; any data that they have is governed by the Medicines Act which means that it’s protected and the public does not have access to it. In this particular case, we were contacted by them because they wanted to coordinate our guideline with their regulatory advice. I think they were keen to ensure that our analysis and interpretation of the evidence concurred with the advice they were about to give. They wanted us to support their advice. They then told us that they were going to publish six unpublished clinical trials on their website.

At the same time, I was passed a confidential internal memo regarding GlaxoSmithKline...the memo was dated 1998. This was six years later in 2004! The memo indicated that there were two trials which had not been published. It recommended that the company should not publish these trials as they showed paroxetine was not effective in treating children who were depressed. These trials have still not been published!

We then decided that we would undertake an experiment in conjunction with the guideline group. We thought, well, guidelines should reflect clinical decision-making. So, we decided to take the meta-analysed published data and say to the guideline group: “If you had the published data only on the SSRIs, would you recommend these treatments on a balance of risks versus benefits?” The guideline group’s response was that, although the evidence from the published data did not suggest that the SSRIs were fantastically effective, on a balance of risk versus benefit they would recommend them as treatments for childhood depression. All of them.

We then took the unpublished trials from the MHRA website, put them together with the published trials, and asked the guideline group the same question. The answer that came back was, with the exception of fluoxetine, or Prozac, the guideline group would not recommend them on the basis of a balance of risks and benefits. The reason for that was, adding in the unpublished data, the apparent effectiveness that you saw with the published trials disappeared. Given that they weren’t effective, and there was evidence in the

trials of a significant increase in self-harming behaviour (roughly two and a half times that of placebo in most of the trials), the risks outweighed the benefits and we wouldn't have recommended them. We subsequently published our findings in *The Lancet* and it caused quite a media furore in the UK and in the United States (see Whittington, Kendall et al. 2004; Whittington, Kendall et al. 2005) (Kendall and McGoe 2007: 132-133).

As Kendall notes, there was much media interest in what was, for many, the first time observers realized that those who are commissioned to produce NICE guidelines do not have legal access to the same clinical trial data as regulators at the MHRA. As an editorial in *The Lancet* noted:

Is it hard to imagine the anguish experienced by the parents, relatives, and friends of a child who has taken his or her life. That such an event could be precipitated by a supposedly beneficial drug is a catastrophe. The idea of that drug's use being based on the selective reporting of favourable research should be unimaginable...in a global medical culture where evidence-based practice is seen as the gold standard for care, these failings are a disaster. Meta-analysis of published data supports an increasing number of clinical decisions and guidelines, which in turn dictate the use of vast levels of health-care resources. This process is made entirely redundant if its results are so easily manipulated by those with potentially massive financial gains (Lancet 2004: 1335).

To date, there has been little sociological or medical attention to the inability of bodies such as NICE and the National Collaborating Centre for Mental Health to access clinical trial data and how that affects the development of clinical practice guidelines. One recent exception is a study from Jorgensen and colleagues, which compared meta-analyses developed by the Cochrane Collaboration, to meta-analyses developed by industry, and concluded that those funded by industry should be "read with caution as they were less transparent, had few reservations about methodological limitations of the included trials, and had more favourable conclusions than the corresponding Cochrane reviews" (Jørgensen, Hilden et al. 2006). The *British Medical Journal* received a number of letters to the editor critiquing Jorgensen's piece – not for casting doubt on the integrity of industry sponsored meta-analyses, but for suggesting Cochrane analyses were free of the

methodological biases that often plague industry reviews. This suggests, unsurprisingly, the “everyday” clinicians and epidemiologists who penned the letters to the *BMJ* are more conscious of the problems stemming from lack of legal access to RCTs than most sociological observers of EBM. Even in detailed discussions of the guidelines movement outside the UK, such as Heimer and colleague’s historical overview of the development of outcomes research and clinical practice guidelines in the United States (Heimer, Petty Coleman et al. 2005), there is no discussion of how the problem of the underreporting of trials affects the evidence base of guidelines. In the UK, the interview above with Kendall has been one of the first empirical glimpses of how selective trial disclosure affects the NICE guidelines-forming process.

Kendall’s experience in developing NICE’s pediatric guidelines for depression raises the question of how, given the constraints facing the MHRA’s disclosure of unpublished trials, news of the unpublished SSRI data in children managed to reach the public at all. Once again, it was an anomaly in typical procedure that led to the publication of the trials. In the early months of 2003, the MHRA launched its sixth safety review of SSRIs, convening an expert working group, a sub-panel of the Committee on the Safety of Medicine (CSM), to investigate the safety of the drugs. This was the panel that Richard Brook was asked to serve on. During the first meeting of the Working Group, Brook was shown confidential clinical trial data testing SSRIs in children. Like most medicines, SSRIs are licensed for use in adults, and prescribed “off-label” for children, which means they have not been specifically licensed for use in under-18s, but are prescribed at a GP or a specialist’s discretion. In the view of my informants, GSK was seeking to change this by requesting a

specific license for children. In May 2003 the company sent a confidential dossier to the MHRA containing previously undisclosed trial data.

Surprisingly, it appeared that GSK had managed to overlook what the regulators soon discerned: GSK's own clinical trial data revealed the drug was not efficacious in children. Still more surprisingly, it revealed that more children were self-harming and experiencing more suicidal ideation on the active arm of the trials than on the placebo arm (BBC 2004). According to media reports at the time, the finding led the MHRA to take immediate action. The Panorama documentary *Taken on Trust* notes that when faced with the new evidence from GSK, "the MHRA acted quickly. Within a fortnight Seroxat was banned for use in depressed children" (BBC 2004: 4). Although my findings from interviews do not conflict with Panorama's reporting of events, they do suggest more internal conflict at the MHRA than was revealed in media stories. During my interview with Brook, he suggested that the information about Seroxat was leaked to the media by an internal source – against the MHRA's wishes.

RB: The Seroxat announcement on the children came out in June. And that was leaked. And there was a leak inquiry. I was quite shocked really about how I was dealt with...I was just very disturbed about the way I was questioned. I mean, as I understand it, about 30 or 40 people were interviewed. I was really surprised because they spent more time trying to chase the leak down than trying to make sure the information about Seroxat got out into the public.

Kendall said he was flabbergasted by the chain of events that led to the realization that his team at the National Collaborating Centre had inadequate trial data, and that companies had deliberately withheld unpublished data, lying to Kendall's team about the existence of unpublished data. He and others I spoke with said they were particularly disturbed by the appearance of memos that suggested certain companies had suppressed trial evidence because of commercial concerns,

such as the internal memo from GSK that stated it would be commercially unacceptable to reveal that paroxetine was not efficacious in children. Increasingly uncomfortable with such developments, Kendall said he persisted in the effort to convince the MHRA to release some of the unpublished clinical trial data that would enable policymakers to obtain a clearer picture of SSRI safety, in both children and adults.

TK: One interim way, which we're exploring with the MHRA, is if they could tell us – because they're allowed to release some information if it's in the public interest – so, if they could just tell us how many trials are published and how many participants are unpublished, that's all we would need to know. If we know that, then we can know what proportion of the total evidence we've got. If we're got 95% of it, then it may be reliable. Do you see what I mean? We should be able to make a calculation. Because it's all numbers. We should be able to calculate the likelihood that we're recommending the right or the wrong thing.

LM: Are you optimistic that the MHRA will go for that?

TK: I'm not very optimistic. I think it would be a simple thing to do. If the MHRA would agree to it. And there are people at the MHRA who would love to give us that information. But they're going to have to see whether they're allowed to (LM interview with Tim Kendall in February 2005).

The motif that emerges from the excerpt above exceeds that of negotiation. In my interview with Kendall and other practitioners, I had the sense that he was almost pleading with regulators, begging them to provide him with the information that would allow him to carry out his NICE-commissioned research. I asked him whether he was surprised by his growing awareness of the difficulties in accessing trial data: “Ten years ago,” he said, “I wouldn't have dreamed we'd be here. Absolutely wouldn't have dreamed it...but the MHRA are bound by laws that haven't changed.” A number of times during the interview, Kendall reiterated that he felt a key problem surrounding clinical trial dissemination was the stringency of the laws preventing the release of commercial data:

When the Expert Working Group [on SSRIs] put the trials up on the MHRA website that was the very first time the MHRA had *ever* released unpublished

trials. They had never, ever done that before. And I think the government needs to repeal the law which says you can get put away for two years if you do (LM interview with Tim Kendall in February 2005).

As Kendall himself noted, however, the existence of the 1968 Medicines Act is simply one of a number of barriers affecting a practitioner's ability to access clinical trial information. A second obstacle is the fact that manufacturers are not legally bound to disclose trials carried out by a company which they acquired via a merger, as this extract from my first interview with Kendall illustrates:

TK: 200 hundred of the [Seroxat] trials still haven't been seen. Now, GSK say that's because they were done before they became GSK. It's a problem with these mergers into bigger and bigger companies because sometimes the trials were done originally by a little company.

LM: A lay person like myself would assume they'd have to assume culpability for something that they merged with, or a company that's been acquired.

TK: Well, they should do. But they claim they don't always have easy access to the data. Because, there are storehouses full of data. I mean, imagine 400 trials of Prozac in adults. Why do you need 400? Unless we're talking about –

LM: 300 that showed no efficacy.

TK: Well, absolutely...it's cherry picking the results and publishing those (LM interview with Tim Kendall in February 2005).

Once or twice during my interviews, respondents expressed an opposite view to Kendall. They saw it as reasonable that there should exist corporate laws to protect the corporate property of trials, and given the existence of such laws, understandable that GSK should have withheld data indicating SSRIs were harmful in children. During an interview with Stuart Donovan, a practicing epidemiologist, for example, Donovan said the following:

SD: GSK are being punished for not declaring something that wasn't relevant to them anyway. Maybe they should have come out and said [something].

LM: Do you think they should have or no?

SD: Oh, that's a judgement. You are asking me to judge. If they had seen something in children that was harming them in some way, they took the view

that, well [we're not going to market the drug], so we don't need to tell anybody. That's clearly a marketing [decision]...[Perhaps] they should have said something a little more strongly, like, I don't know what the label says, but, it should have been, do NOT give to children under twelve, rather than, children under twelve – not recommended (LM interview with Stuart Donovan in February, 2005).

This respondent, who expresses a degree of ambivalence on the question of voluntary clinical trial disclosure, was in the minority of the practitioners and scientists I spoke with. The majority were unequivocal in echoing Kendall's frustration surrounding the pharmaceutical industry's retention of unpublished trials, as well as the constraints on the MHRA's ability to release trial data to the public.

In March, 2005, I spoke with Susan Bailey, a child and adolescent forensic psychiatrist for the Salford, South London and Maudsley NHS Trusts, a senior research fellow at the University of Manchester, and former chair of the child and adolescent faculty of the Royal College of Psychiatrists. Early in the interview, Bailey stressed the difficulty noted earlier: the fact that, like many paediatric medicines, SSRI antidepressants are prescribed "off-label" for children and adolescents under-18. One of the things contributing to the lack of licences for a medicine's use in children is that there are often far fewer RCTs testing a medicine in children than in an adult population, and so the evidence base is smaller for regulators to scrutinize when trying to determine a risk-benefit profile.

The following excerpt describes Bailey's growing discomfort with the lack of RCTs in children, as well as her efforts to lobby the MHRA to release the clinical trial that had been carried out. The following are the comments which Bailey said she was comfortable making on record. Twice during our interview she asked me to switch off the tape while she described more personal comments about her specific relations with the MHRA – comments she was not willing to voice publicly.

I became concerned about SSRIs in the forensic context, because of reports that children were becoming agitated and aggressive. By then, I'd become chair of the child and adolescent faculty, so it was well under my remit. We, as [an executive faculty of the Royal College of Psychiatrists] became increasingly concerned about the way information was dribbling out, and it was making us less and less sure about the benefit ratio of these medications in young people. We started to lobby quite heavily to meet with the MHRA in our own right. Each meeting we had with the MHRA we were given assurance that things were on track...I think what we've found frustrating, looking at systems, is that nobody has a complete handle on this. So, the MHRA and the CSM, they're very specific. They talk in technical language...the guidance is still put out in very technical terms which is open to misinterpretation and which, I think, we as professionals and practitioners were made to feel rather stupid (LM interview with Susan Bailey, March 2005).

Bailey's disillusionment with the MHRA's treatment of her request for clinical trial information was echoed by Shooter, then president of the UK's Royal College of Psychiatrists. I met with Shooter in May 2005. In the following excerpt he describes some of his concerns with the MHRA:

LM: I have heard there is fear among individual [MHRA staff] of litigation from pharmaceutical companies for the release of confidential data.

MS: I can understand the fear of litigation. Because there are individual people – very, very brave people – who, for the last number of years, have been in and out of the courts themselves. Either advising people who are part of court cases, or themselves being taken to court for what they have very bravely said, openly and in public. And I think those people deserve our full admiration. For taking that risk. That cannot have been very comfortable. So, if there are people within the regulatory bodies that fear legislative comeback – but heavens it's their *job* to be tough! If they fear that, what are they *doing* in that job, for heaven's sake? It's their *job* to be tough. They are supposed to be the policemen of the drug industry. They can't go around being frightened by that! (LM interview with Michael Shooter, May 2005).

Shooter's concern was shared by most of the clinicians I spoke with. They seemed bewildered by both industry tactics, and by the extent to which, as Woods noted himself in our interview, the role of the regulator was primarily a dialogue with industry. To conclude this chapter, I return to Woods' comments on the MHRA relationship with industry, providing more context to his earlier quote:

KW: The further I go in this job, the more I see that actually the social aspects of what we do are very important. In the sense – just as a final comment: when I

came into this job, the relationship, the role of the regulator was seen very much as a dialogue with industry. You bring us a product, we'll tell you whether you can market it, end of story. Actually, it's a far more complicated relationship than that. We have an external constituency – the public and patients. And most of our job is actually putting out good quality information on the risks and benefits of medicines, on which patients and prescribers can make wise, informed decisions. That has never been seen, up until a few years ago, as the role of the regulator.

LM: Okay. I would have thought it would have been the opposite. 'Safeguarding public health' is a maxim of the MHRA. I would have thought the reverse of that would be the case.

KW: No. There are two things a regulator can do if it feels that a product has a difficult, or borderline, or complicated risk-benefit relationship. One is that it can say, this product shall not be marketed, it shall not be sold, it's gone. Now, that actually – although it might be an appropriate step to protect public health, what does it do for patient autonomy? I have lots of letters in my mailbox saying, "How on earth can you take coproxamol off the market simply because 200 people a year choose to commit suicide with it? I like coproxamol, it's good for my joints. How can you deprive me of the opportunity to use coproxamol?" We've done it because we feel that's the right answer for public health...the most important thing that we do is actually make sure that prescribers and patients have got the evidence on risks and benefits to make their own judgement. If you want patient autonomy, you need informed consent. You can only have informed consent if people have got the information they need, which is unbiased and accessible.

At first glance, Woods's comments seem defensible, and help to soften the starkness of his earlier comments on the relationship of the MHRA to industry. His assertion of the need for open and accessible clinical trial data is contradicted, however, by his position earlier in the interview, when I asked him about the key concern of people such as Kendall, Bailey and Shooter: the fact that the MHRA has more legal access to trial data than places such as NICE:

LM: Would you like to see a move to a system where NICE had access to the same data as the MHRA?

KW: No.

LM: Why not?

KW: It's important to understand firstly what NICE is there for. NICE is an NHS organization. Its job is to give advice and guidance to the NHS. I mean, the NHS is just a very large Health Maintenance Organization. We have a statutory responsibility to the nation as a whole, and therefore our remits are somewhat different. The second thing is that it is far preferable that we are able to communicate to NICE at a confidential level, so that NICE is able for instance to organize their work programme, and to plan when a product is likely to come up for appraisal, than NICE having access to the raw data that we see.

LM: As a former clinician yourself, as an epidemiologist, are you worried about what people like Chalmers have talked about, which is the general integrity of evidence bases.

KW: I know one of the things that bothers Iain [Chalmers]. And maybe this is what he has referred to. That companies submit to NICE the data they chose to submit. They submit to us, under legal obligation, all the data they have. And so, in a way, NICE is working at a disadvantage. And always has worked at a disadvantage, because it hasn't had the statutory power to demand all the evidence that companies own. The way we got around this when the appraisal process was being set up – and I was director of the Health Technology Assessment programme then – we undertook that we would commission independent, academic groups to weigh all the available evidence, whether it's in the company...or published evidence, so that there was an independent meta-analysis or systematic review that went to NICE, alongside the company's synthesis of its evidence. And that actually built into the NICE process a degree of external corroboration. Now, that was a very carefully constructed process. And I think it's worked incredibly well.

Most of the individuals I spoke with, such as Kendall, co-director of the NCCMH, one of the “independent, academic groups” referenced by Woods – do not agree with his opinion here. They argue that without authority to elicit trials from industry and academic sources, the effort to build “a degree of external corroboration” into NICE has failed.

Conclusions

My interviews with policymakers and clinicians revealed that many individuals consider the legal framework surrounding access to clinical trials information to be an impediment to formulating reliable clinical practice guidelines. Combined with their frustration over access to data has been the belief that the UK's drugs regulator is not acting in the interest of patients. I referenced Foucault in order to highlight what I repeatedly found in interviews: a sense of deep anger, bewilderment and frustration at the actions of the MHRA. What seems to frustrate clinicians in particular is that despite widespread recognition of the MHRA's earlier

failures, the regulator has remained the sole authority with access to the very clinical trial data that the regulator failed to disclose swiftly in its earlier SSRI inquiries.

In many ways, recognition of the MHRA's ineffectiveness is widespread. As quoted earlier, a key finding of the Health Select Committee's recent inquiry into the pharmaceutical industry was that: "Regulatory inertia was clearly illustrated through the findings of the UK's first ever public investigation into a drug safety problem: the December 2004 report of the CSM's Expert Working Group (EWG) into the safety of SSRI antidepressants" (HOCa 2005: 19).

Despite widespread recognition of the MHRA's mismanagement of its SSRI inquiries, there has been little improvement in the agency's transparency, and no accountability for earlier mistakes. The key problem illuminated by the SSRI case – the inability of policymakers to access data – remains unchanged. As Kendall said, "we need to see all the trials. Until the regulators have the power to ensure this, I think we will always be unsure about the evidence base [of all NICE guidelines]...I think it is absolutely necessary for physicians, psychiatrists and indeed the public, to publicly and forcefully say that this is completely unacceptable. This threatens the evidential basis of contemporary medicine. It is nothing short of a battle for truth" (Kendall and McGoey 2007: 139-140).¹⁴

Kendall's experience resonates with Foucault's reversal of Clausewitz's aphorism. In the case of the SSRI controversy, the process of policy formation has taken on the proportions of a battle. The winners and losers have been those with the superior access to the key tools or "weapons" in medicine today: randomized

¹⁴ This relates to forthcoming work by David Demortain, who argues that rather than producing change, drug crises in the UK have tended to provide political legitimization and funding opportunities for previously held strategies that are only recast as solutions in retrospect. Crises tend not to lead to novel solutions, particularly as "regulatory change is determined by the action of a group which, ironically, is likely to minimise the novelty of lessons publicly drawn from the crisis in an attempt to defend its ownership and minimise its responsibility" (Demortain 2008).

controlled trials. In the next chapter, I develop a theoretical framework that seeks to explain why RCTs continue to command such political and medical authority despite the fact, as this chapter has indicated, so many political factors affect their construction and use.

Chapter Six: The moral authority of randomized controlled trials

Introduction

“It would be nice,” Bruno Latour writes in the opening line of the essay *Visualization and cognition: thinking with eyes and hands*, “to be able to define what is specific to our modern scientific culture.” What are the plausible phenomena, he asks, that can explain some of the leaps in scientific, technological, literary and economic achievements over the past three or four centuries? Hypotheses about seminal changes in human “mentality,” or in the structure of the brain, or in sudden shifts in economic infrastructure, often seem too grandiose: “no ‘new man’ suddenly emerged sometime in the sixteenth century...the idea that a more rational mind or a more constraining scientific method emerged from darkness and chaos is too complicated a hypothesis” (Latour 1986: 2). In favour of grandiose theories, Latour argues instead for “more parsimonious accounts, which are empirical through and through, and yet able to explain the vast effects of science and technology. It seems to me that the most powerful explanations, that is those that generate the most out of the least, are the ones that take writing and imaging craftsmanship into account” (3). Latour’s aim in the essay could be summarised in a single line: he seeks to develop a theory of the social authority of technological representations in order to account for technological and political change.

Drawing on Latour’s concept of inscription devices and immutable mobiles, as well as work by Jack Goody on literacy, and Maurice Bloch on the limits of Goody’s argument, the aim of this chapter is to explore the moral authority of randomized controlled trials in arbitrating during periods of medical debate and controversy. The

primacy of RCTs within evidence-based medicine, I suggest, can be explained by comparing them to immutable mobiles: devices of persuasion and political mobilization, much of the authority of which can be attributed to their efficacy in compressing large amounts of data into smaller and more mobile pieces of information, allowing themselves to be more effectively distributed among larger and larger territories.

The structure of this chapter is as follows. Firstly, I apply Latour's concepts of inscriptions and immutable mobiles to an analysis of RCTs. Secondly, I turn again to the controversy over SSRIs in order to explore the efforts of British medical practitioners to develop a better understanding of the safety of SSRIs through recourse to the published SSRI clinical trial data. Finally, drawing on the work of Maurice Bloch, I suggest that a misperception of the role of social and political relations in arbitrating on the access, use and deployment of new technologies has led to a misunderstanding of the usefulness of RCTs in providing both clinicians and patients with a better understanding of the safety and efficacy of the treatments.

"What's in a list?", anthropologist Jack Goody has asked, arguing in part that lists, like other forms of representation, enabled things to be collated, classified, and above all both transcribed and transfixed – immobilized for the scrutiny of successive generations: "When an utterance is put in writing it can be inspected, manipulated and reordered in much greater detail" (1977: 44). It could thus be challenged. The process of transcription, Goody surmises, helped to pave the path toward political rebuke and dissent. By distancing an idea from the arbitrary authority and influence of its origins, the idea is rendered more open to the scrutiny of observers who otherwise might have been forced to acquiesce to the authority of

whomever had voiced the idea. The process of transcription, in other words, renders an idea more politically challengeable; ideas that are recorded are:

subjected to a quite different type of scrutiny and critique than is possible with purely verbal communication. Speech is no longer tied to an 'occasion'; it becomes timeless. Nor is it attached to a person; on paper, it becomes abstract, depersonalized" (Goody 1977: 44).

Goody's view is reminiscent of the statistician Ronald Fisher's early hope that the transcription of statistical experimentation would allow everyday, thinking men to reach their own conclusions about a given phenomena (Fisher 1935: 2). Strong echoes can be heard among the EBM proponents who believe that fostering greater access to RCTs will help to democratize clinician-patient relations, encouraging the ability to challenge the authority of treatments based solely on a clinician's eminence or experience. The thought is both so logical, and so appealing to those who value democratic opportunity, that one is almost reluctant to point out the ways that they have been wrong.

Parsimonious changes: Latour and the rhetorical authority of representations

"Who will win in an agonistic encounter between two authors?" Latour asks at the start of the essay *Visualization and cognition*. His answer:

The one able to *muster on the spot the largest number of well aligned and faithful allies*. This definition of victory is common to war, politics, law, and, I shall now show, to science and technology. My contention is that writing and imaging cannot by themselves explain the changes in our scientific societies, except insofar as *they help to make this agonistic situation more favourable* (1986: 6).

Goody's work on literacy, Latour writes, had the merit of illustrating the importance of simple craftsmanship, of simple inscription, in fostering the tools that would enable individuals to both challenge and cajole the opinion of others, to

persuade in matters of dispute, and to defend one's decisions whenever someone else calls them into doubt. When he first stepped into a biological laboratory, for example, Latour found that:

the domestication or disciplining of the mind was still going on with instruments similar to those to which Goody refers. When these resources were lacking, the selfsame scientists stuttered, hesitated, and displayed every kind of political or cultural bias. Although their minds, their scientific methods, their paradigms, their world-views and their cultures were still present, their conversation could not keep them in their proper place. However, inscriptions or the practice of inscribing could (4).

This observation does not lead Latour to argue that it was the inscriptions themselves that carried inherent efficacy as rhetorical props and tools, but to suggest that the essential characteristic of any inscription was its usefulness as a tool of mobilization. It was not the mere existence of an inscription that matters, but its potential as a durable tool of persuasion. A map drawn in erasable chalk, or in shifting sand, is less useful – less *powerful* – than a map which can be duplicated, photocopied and sent to others. To be authoritative, Latour suggests, an inscription should have the five characteristics of being *mobile*, *immutable*, *presentable*, *readable* and *combinable* with other things (1986: 7).

Latour elaborates through drawing on Elizabeth Eisenstein's (1979) study of the printing press, an analysis which can be commended, he argues, for illustrating – against suggestions of a grand, dichotomous shift – that before the advent of print, most seemingly modern, scientific developments such as organized scepticism and systematic data collection had been sophisticatedly developed in different, separate locales.

The advent of print and the printing press changed little except for the transportation of these achievements. Previously, new advances remained local and “temporary just because there was no way to move their results elsewhere and to

bring in those of others without new corruptions or errors being introduced” (1986: 12). With the press it became possible to compare and contrast the inscriptions once kept geographically separate, facilitating the inspection, correction and propagation of errors.

In the now familiar argument, technological progress thus emerged in part as a side-effect of the material dissemination of inscriptions. But what led, Latour asks, to the press’s development in the first place?

His answer: by casting Eisenstein’s argument in terms of immutable mobiles, one can observe that anything that carries the characteristics of being useful in agonistic situations, anything that accelerates the mobility of traces, that allows traces to move from one place to another without transformation or corruption, that are durable, representative, replicable and combinable, will be favoured over the things which die as soon as they are spoken, or which wither in the process of being transferred away.

Latour adds another observation, one which is relevant to explanations of the rhetorical authority of randomized controlled trials, both in their individual form, and even more crucially, in their combinable form with other RCTs in meta-analyses. The authority of inscriptions, Latour argues, lies in being combinable with other inscriptions in a way that *augments* the strength of the numbers or concepts behind the inscription, while simultaneously *simplifying* their visual representation to those whom one wishes to convince.

“The trend towards simpler and simpler inscriptions that mobilize larger and larger numbers of events in one spot, cannot be understood if separated from the agonistic model that we use as our point of reference,” Latour asserts, arguing that critics who ignore this agonistic starting-point miss the point of the concept. Some

have suggested, for example, that Latour's concept of inscriptions is not a helpful heuristic, because for every representation there exists a myriad of possible interpretations. Although in theory this may be true, "in practice this is far from being the case; the cost of dissenting increases with each new collection, each new labelling, each new redrawing...for each "objection" there is an inscription that blocks the dissent; soon, the dissenter is forced to quit the game or to come back later with other better and visual displays (1986: 18-20).

Not only must the displays be better, they must be phrased in the language or transcribed in the codes stipulated by the individuals one wishes to engage with and convince. As I suggested earlier, those in authority generally dictate even the forms of resistance which the authority has provoked in the first place. This insight helps to nuance a criticism sometimes suggested of RCTs, which is that individual studies are often useless in practice, because different practitioners regularly read the results in competing and variable ways, taking any number of different interpretations from the same study. What this criticism fails to realize is that the multiplicity of possible interpretations does not *reduce* the rhetorical authority of RCTs. In fact, it *strengthens* their legitimacy: because to deny the validity of a particular study, one must reach for ever more data, ever more studies, ever larger RCTs in order to justify that one's interpretation is more credible than the interpretation of another.

Thus, criticisms of the calculations or the interpretations in a given study tend to cement the faith that more numbers are needed to clarify the problem. One is always free, of course, to suggest that numbers alone are incapable of arbitrating in the debate at hand, or that it is the numbers themselves that are the problem – but what data, what representations, what visuals, what inscriptions does such a dissenter have at hand to convince others of the value of her interpretation over others? The

problem is not that one is barred from speaking, but that, until one has the capital to adopt the acceptable methods, one's interlocutors are equally free to remain deaf. With these thoughts in mind, it is possible to return to an analysis of the political usefulness of RCTs within evidence-based medicine.

EBM, internal dissent and the demand of objectivity

In March, 2006, I met for a joint interview with Iain Chalmers, a leading figure in the development of evidence-based medicine in Britain, and currently the editor of the James Lind Library, and Paul Glasziou, head of the Centre for Evidence-Based Medicine at Oxford University. During a series of interviews I had been conducting with psychiatrists, I told them, I had been particularly struck by how often two psychiatrists with competing perspectives on whether SSRIs contributed to suicide would point to the same study as proof of their disparate positions:

LM: Does that surprise you or no?

IC: No.

PG: Tom Chalmers used to say – this is 20 years ago – about the need for systematic reviews, that if you talked to a physician they would point to the trials that show medical therapy worked better, if you talked to a surgeon they could point to the trials that said surgical therapy worked better. People select the trials that show the result that they want. So, I often get people wanting to learn about EBM because they say, I want to find the evidence that supports such and such. They're actually looking to be able to search more efficiently for the bits that they want.

Does that not pose, I asked them, a problem in general for advocates of evidence-based practice? If the problem of selection and interpretation bias is so pervasive, why the push for ever larger databases of RCTs, which are then left to the varying opinions of individual clinicians? There are moments when one is interviewing individuals with vastly different specializations that a disjuncture seems to threaten the amiability of the exchange, not as a result of any overt hostility, but

merely as a result of an utter, blank-faced lack of comprehension for the view-point of the person opposite. They looked at me in bewilderment for a moment. That is precisely *why* the push for evidence-based practice is so relevant: to minimize treatments based on whim, or the systematic selection of the results that most suit one's prior hypotheses or judgements. The desire to minimize biases in the design and use of RCTs (biases which, as Chalmers aptly stressed in our interview, most sociologists, lacking the technical expertise of statisticians and epidemiologists, "haven't even *thought* of") has been a founding impetus behind the evidence-based practice movement.

If Chalmers and Glasziou were critical of sociologists during our discussion, they were also critical of what they saw as the appropriation of the evidence movement by bodies such as NICE in order to justify the rationing of treatments for reasons of cost effectiveness:

PG: The Sackett version of evidence-based medicine is purely clinician-patient autonomous. It's the clinician and patients making the decision, being informed by the evidence. That's what he was preaching at McMaster. That's what the McMaster folk are teaching. But there's been a lot of interpretation of evidence, people....stealing that phrase. And then using it to mean guidelines that are created by some committee, that are then imposed upon clinicians, removing both the clinician and – importantly – the patient's autonomy.

LM: Who is responsible for that? The people who set up NICE?

PG: The movement to guidelines around the world has largely been led by some interest in evidence-based practice, but also in economic issues. Trying to constrain physician practice because of the growing costs. Because of an interest in that, governments around the world have sponsored the production of guidelines. With NICE just being one example. The US set up all these evidence centres to produce and generate guidelines. The Canadians have similar things. So, health technology assessment and guideline production has been a booming industry. Which people have labelled evidence-based medicine.

LM: And you think it's a usurpation, basically.

PG: Well, it's almost a stealing of the term.

Both Chalmers and Glasziou stressed frustration with the fact that sociologists and other analysts have largely failed to scrutinize the internal divisions within the

evidence-based practice movement. Another frustration is that many sociologists have failed to gauge the high level of self-criticism among EBM proponents themselves, for both the ways in which their research has been taken up by government bodies, as well as for the many methodological obstacles towards obtaining more scientifically reliable evidence. Sociologists have often approached such methodological obstacles, such as the retention of unpublished trials by industry, as something which they have only recently managed to unearth, which fails to consider that controlling for methodological biases was a founding impetus behind evidence-based practice to begin with. As Chalmers noted during our interview:

IC: In some senses a criticism of the Cochrane Collaboration which implies that they're not worried about [selection bias] is a misrepresentation. Because in fact, most of the biases that have been unearthed in the evidence-generating and evidence-dissemination process have been unearthed by people who do systematic reviews. And they ought to bloody well get credit for that! I'm not suggesting that you wouldn't give them credit. But I am suggesting, the way that some people present it, it's as if it's their discovery.

If this high level of methodological self-criticism lies undetected in the majority of sociological analyses of EBM, it is perhaps because, notwithstanding a few exceptions such as Chalmers, EBM proponents are often seen as propagating a seemingly impervious aura of certainty in their own methods, as is implied in Daly's proposal, which I mentioned earlier, of a "hierarchy of evidence" for qualitative research. Throughout this thesis, I have suggested this founding premise of EBM – that increasing the scientific base of medicine will increase its equity, effectiveness and efficiency – has been integral to the emergence of what I describe as the moral authority of objectivity within medicine. My aim has been to explore the implications of objectivity's moral authority for both practitioners and regulators. How have practitioners responded to the increasing need to defend treatment decisions with

recourse to RCT evidence, and not to personal clinical observations? How have regulators profited (or suffered) from the effort to standardize licensing procedures in line with RCT methodologies? How do individuals voice dissent within the constraints of an evolving model of medicine which has seen the professional authority of medical bodies such as the Royal College of Psychiatrists challenged by the increasing authority of places such as NICE?

When individuals do voice critiques, it seems they are often – as David Healy has been – penalized professionally and personally for bringing politics to medicine, something viewed as particularly offensive given the collective efforts to rid medicine of personal interest. In its purported quest to minimize the influence of personal or political interests on medicine, the rise of EBM has, in some ways, succeeded. Individuals face much professional scrutiny if they vary from NICE guidance in their clinical decisions, or if they attempt to argue, as Healy did, that the established perception on a treatment's safety is wrong.

Where proponents of EBM are misguided, however, is in the suggestion that by curbing the political influence of individual practitioners there has been an elision in general of politics and political manoeuvring from medicine. As the sociologist and clinician David Armstrong has noted in a recent article on the influence of EBM in reducing uncertainty within medicine, EBM does not dispense with uncertainty – it merely shifted questions of uncertainty to, among other things, the interpretation of trial results (Armstrong 2007).

Despite the hopes among many that the rise of EBM would democratize access to clinical trial data, rendering clinician-patient relations less hierarchical, that hope has not, at least in the case of debates over SSRIs, come to pass. Instead the sources of authority have shifted from clinicians to the regulatory complex

overseeing the dissemination and disclosure of clinical trial information. Today, political and professional debates over the safety of drugs are increasingly centred on the most technical of questions, on things such as the inclusion of patients on trials, the propriety of the recording of clinical trial data, and the validity of the measurement scales used in trials.

Paradoxically, it is this technical arena – the very arena that has become the *most* political in debates over the safety of medicines – that is simultaneously the *least* universally accessible, not simply to patients and other lay observers, but to most practitioners themselves. That, in short, is the dilemma which I noted above. The problem is not simply that the growth of objectivity in medicine has shifted political questions to a more technical domain. But that in doing so it has rendered it more difficult for practitioners to contest that shift *except through access to the very data which that shift has rendered more inaccessible*.

This exclusivity of method – the inability to critique a dominant methodology without the capital to adopt the methodology itself, is at the heart of why Goody, Fisher and others have been wrong, or at least short-sighted, in their equivalence of transcription – the transcription of lists, in Goody's view, and statistical analyses, in Fisher's – with political empowerment. This relates to work by Thrift, who has observed, in an analysis of political literacy in 19th and 20th century Britain, that there are not necessarily correlations between the availability of political information in the form of political pamphlets, chapbooks and newspapers, and the ability of individuals to act politically on newfound information. Often a lack of symbolic or cultural capital prevent the ability to act on information, regardless of how freely the information is physically available (Thrift 1985). In the following sections, I support this observation by returning to the SSRI controversy.

Political struggles over the access, interpretation and use of trial data

During my first interview with Tim Kendall, I asked his views on the realization that NICE does not have legal access to the unpublished clinical trial data that had a bearing on treatment guidelines.

The truth is, the whole of the evidence-based medicine movement was worried. The evidence-based guideline movement absolutely hinges on the published evidence. If people can hold back, and not publish, it would just undermine the whole lot. I mean, evidence-based practices good-bye.

Kendall's comment parallels the *Lancet* editorial which I quoted in the previous chapter: "Meta-analysis of published data supports an increasing number of clinical decisions and guidelines, which in turn dictate the use of vast levels of health-care resources. This process is made entirely redundant if its results are so easily manipulated by those with potentially massive financial gains" (Lancet 2004: 1335). A number of EBM proponents themselves – particularly Chalmers – have stressed the same point. Chalmers has lobbied for over fifteen years to increase the legal onus on the pharmaceutical industry to register all clinical trials at their inception – which would limit the ability to hide or bury findings unfavourable to the products they wish to market. In a number of articles, Chalmers has gone as far as to argue that the withholding of company trials should be treated as scientific misconduct (Chalmers 1990; Chalmers 2006). Despite this, many of the proponents I spoke to did not view the lack of onus to register trials as undermining the ethos or aims of evidence-based medicine. It only heightened the need to better interact with the pharmaceutical industry in order to persuade them to work more collaboratively with clinicians and scientists in order to get better understandings of the safety and efficacy of drugs.

In February 2005, I met in the lobby of London's NICE offices for an interview with John Geddes, a professor of psychiatry at Oxford University and head of the Centre for Evidence-Based Mental Health. During our hour-long interview, Geddes took care in describing why critics who thought the controversy over SSRIs has undermined evidence-based medicine did not understand the EBM movement. Geddes firstly stressed an apt point: the need to recognize the extent to which the patient inclusion criteria of any RCT has an influence on the clinical usefulness of results.

As noted earlier, since the 1960s, US and UK regulators have stipulated that all new medicines must be tested for safety and efficacy through RCTs in order to earn licences. The need to test substances via the methodology of RCTs raises, as the anthropologist Andrew Lakoff notes, specific challenges for the development of psychiatric drugs, where, in order to determine whether a patient is eligible for enrolment in a trial for, say, a new antidepressant drug, one first has to determine whether the patient *has* depression, and its level of severity. This is notoriously difficult for psychiatry, where the process of diagnosing patients often varies between different clinical observers. In response to this, psychiatric researchers have developed questionnaires and rating scales, the most familiar of which is the Hamilton Depression Rating Scale (HAM-D), where behaviour and mood is codified and categorized according to standardized checklists. Patients receive a score for responses to questions about mood, insomnia, sexual function and so on – and the final score is used to help determine the severity of a patient's illness. As Lakoff notes, the point of rating scales is:

To *de-subjectivize* clinical evaluation: rating scales were a method of regulating the actions of doctors and drug promoters against undue influence, either conscious or not. Rating scales freed the act of evaluating therapeutic efficacy from reliance on expert judgement...the ability to quantify the symptoms of

depression by using rating scales thus helped drug researchers to delineate a target population [eligible for enrolment in RCTs] (Lakoff 2007: 61)

When designing an RCT to test a new antidepressant, the need to delineate a target patient that *has* depression is countered by the need to meet the ethical requirements of ethical review boards, which often stipulate that the more severe a person's disorder, the greater the ethical duty to *avoid* placing such a patient in a randomized trial. This is because if they are randomized to the experimental treatment, they are potentially denied access to the best, proven therapy. As a result of this ethical stipulation, as Geddes described to me, much of the available RCT data for SSRIs is "necessarily skewered towards the relatively mild, trouble-free end. Because they're the only people that it's actually ethical to put in."

Geddes's point was returned to a number of times by the practitioners I spoke with. Susan Bailey, for example, noted that "you almost have to be well in the States to get on a trial. Because if you've got anything wrong with you, you get excluded." Stuart Donovan, a British epidemiologist with whom I spoke in March, 2005, noted that he found it unsurprising that GSK's clinical trial did not indicate a link between suicidability and SSRIs because "they select out all the suicide people. That's what you do in clinical trials. There's nothing underhand about that." One of the difficulties raised by the systematic selection of individuals at the less severe end of a disorder or a disease for participation in clinical trials is, as David Healy has stressed, the likelihood of a disconnect between a treatment's performance during a trial, and its performance when distributed clinically. As a number of the practitioners I spoke with pointed out, it is extremely difficult to determine the effect of SSRIs among suicidal individuals, because investigators are barred for ethical reasons from investigating that question through RCTs.

The differences among people such as Geddes, Bailey, Donovan, and Healy do not stem from arguments over whether patient inclusion criteria has a bearing on RCT evidence – all agree that it does. Their differences lie in their conflicting views on how to *respond* to that knowledge. For some, the recognition of the uncertainty of RCT evidence leads them to argue for the need to carry out more RCTs, in the hope of developing more refined evidence. Others argue that a recognition of the precarious nature of RCT evidence calls for an institutional reversal of the premium placed on RCT evidence by regulators and guideline-forming bodies such as NICE.

For individuals such as Geddes, who claim there exists, as Geddes describes, “an unknowable gulf between the results from patients in trials, and the results of people in routine, clinical practice,” the answer is to call for more trials, as well as to apply greater caution in appraising the evidence that is available.

The problem, Geddes’ interlocutors reply, is the question of what resources – of time or expertise – does the practicing clinician have in searching for the best, available evidence, or more crucially – in *contesting* the validity of evidence which they have deciphered as problematic or lacking? Although NICE policymakers examine a variety of different material in formulating clinical guidelines, such as qualitative, narrative evidence supplied by carers and patients during focus groups or individual interviews, “in the first instance,” as Kendall put it to me, policymakers “locate RCTs if they have been done” (Kendall and McGoe 2007: 131). RCTs, although not the sole evidence analysed when formulating clinical guidelines, are usually viewed as the best method for determining which treatments work best in comparison to others. This alone, of course, is not a problem. NICE guidelines are not objectionable because they are based primarily on RCT evidence. NICE

guidelines are objectionable because they are based on RCT evidence that represents only a fraction of the clinical trial data held by manufacturers and regulators.

How large is this fraction? In the aftermath of the SSRI controversy, Kendall wrote to the MHRA to ask for more access to unpublished RCT data. In response, Kendall was:

Given data from the MHRA, not revealing trial signifiers or anything like that, but just lists of trials which tell you how many men and how many women have been in the trials. From this, we have been able to work out the number of trials we have been able to obtain from published sources as a proportion of the published and unpublished trials obtained by the MHRA. Roughly we're getting no more than half...In other words, for the majority of psychiatric drugs, less than half, and maybe only a third on average, of clinical trials are being published (Kendall and McGoev 2007: 132).

Given the fact that NICE guidelines are routinely based on only a small proportion of clinical trial data, there exists a strong possibility of a disconnect between NICE guidelines and the reality of a drug's efficacy and safety in practice. A difficulty emerges when clinicians themselves, through their daily practice, start to decipher this disconnect (from, for example, patients responding in ways that are odds with NICE expectations of treatment effects). When they do detect anomalies, how are clinicians to respond? Professionally, any deviance from NICE guidelines exposes them to potential legal reprimands: as the NICE website stipulates, patients are asked to lodge formal complaints should physicians diverge from NICE guidelines. They can, of course, do more research – comparing their clinical observations to databases available at the Cochrane Collaboration, for example. The problem is that Cochrane researchers equally have no legal access to unpublished clinical trial data. Thus Cochrane reviews are exposed to the same problems as NICE guidelines (see the article, and the responses, from Jørgensen, Hilden et al. 2006). In reality, clinicians have few resources to justify their divergence from NICE

guidelines – they can rarely, for example, stage a large-scale RCT to try and derive supporting evidence. And without such supporting evidence, they have little hope in convincing their peers or their patients of the probity of diverging from NICE guidance. The moral authority of objectivity acts as a barrier towards diverging from the accepted evidence on a given drug – regardless of how selective or flawed that evidence is in the first place.

The point, a proponent of evidence-based medicine is justified in responding, is that the benefit of curbing a practitioner's ability to act according to his personal whim, or to his partisan allegiance to a particular brand or company, *outweighs* the subsequent blow to his ability to counter the established views on a treatment. After all, a goal of EBM is to challenge, "the paternalistic and authoritarian nature of much medical practice" (Liberati and Vineis 2004). EBM is seen as providing a solution, as I noted earlier, to "the problem of drug company influence over medicine: limitations on professional and patient autonomy are justifiable, because both groups make irrational developments based on commercial marketing" (Saarni and Gylling 2004: 174). It is difficult, however, to view EBM as a solution to the problem of "drug company influence over medicine" when the majority of evidence available at bodies such as NICE is based on the select number of trials made public by industry and by regulators.

The controversy over SSRIs helps to illuminate this point. Above, I have stressed how patient inclusion criteria has an influence on the clinical usefulness of an RCT's results. Another methodological aspect which can influence efforts to interpret and implement trial evidence is the difficulty in extracting individual patient data from manufacturers and regulators.

The term individual patient data refers to the raw data for each study participant in each randomized controlled trial included in a systematic review. Access to individual patient data is considered highly beneficial as one can scrutinize the methods used in compiling aggregate data, as well as examine things such as how the age, gender, and ethnicity of each subject may have affected trial outcomes. Access to individual results is also useful for examining things such as the recording of endpoints by trial investigators. In clinical trials, an endpoint is any event or outcome that is measured by trial investigators to determine whether the treatment under investigation is beneficial. Examples of endpoints include patient survival, improvements in quality of life and the relief of symptoms. When it comes to antidepressant trials, endpoints include completed suicides, attempted suicides, or what is referred to as suicidal ideation – exhibiting disturbing behaviour, or thinking or dreaming repeatedly of suicide.

Despite the fact that in the UK, all drug manufacturers are mandated by law to disclose both raw data and aggregate data to regulators, typically companies do not submit raw, individual patient data. Instead, companies submit what are referred to as summaries of patient data. This tendency was widely questioned in the wake of the SSRI controversy, including by David Gunnell, one of the UK's leading epidemiologists, and a former advisor to the MHRA's 2003-2004 Expert Working Group on SSRIs. Gunnell has argued that increasing access to disaggregated patient data would enable analysts to scrutinize the recording of each for each subject – something necessary in part because of the possibility of the underreporting of trial by on-site clinical investigators.

The need for better access to individual data was highlighted in February, 2005, when a series of three articles were published in the *British Medical Journal*

(Fergusson, Doucette et al. 2005; Gunnell, Saperia et al. 2005; Martinez, Rietbrock et al. 2005). Each of these articles had as their focus the question of whether SSRIs contributed to suicide in some users. Each article systematically reviewed available trial data in Britain, the United States and Canada. Each study came to a different conclusion about the safety of SSRIs.

I conducted the bulk of my interviews with practitioners between February and June 2005, when the three February *BMJ* articles were fresh in many of their minds. As I described to Chalmers and Glasziou during our interview, I found these articles were raised often by practitioners with opposite views on whether SSRIs increase the risk of suicide, who would point to the same article as proof of their separate positions. In March, 2005, for example, I met with David Healy. Early in the interview, he pulled up a picture of the cover of the February 2005 issue of the *BMJ* and pointed to a graph which suggested an answer of “yes,” SSRIs *do* increase the risk of suicide in some users, confirming the position Healy had been advocating for years.

Three weeks later I met with David Nutt, a professor of psychopharmacology at Bristol University and former member of the MHRA 2003-2004 expert working group on SSRIs. Nutt, as I mentioned in an earlier chapter, is of the position that SSRIs do not lead to suicide. Some feel his credibility has been affected, however, by a series of articles in the UK’s *Guardian* newspaper which revealed he has had extensive ties to GlaxoSmithKline and other manufacturers of SSRIs. Nutt was also pleased with the three February *BMJ* articles. As he said to me during our interview:

The suicidal ideation story was interesting. But the latest *BMJ* stuff clearly shows that it doesn’t cause suicide. So that’s it. So, it doesn’t cause suicide. Now we know. It will never – with those numbers – if it hadn’t by then, then it never will. And I didn’t ever believe it did. The suicidal ideation I’ve certainly seen in some people. But it *doesn’t* cause suicide (LM interview with David Nutt in March, 2005).

Nutt is referring to the large numbers within the trials reviewed by the three BMJ meta-analyses, and to the seeming statistical authority that stemmed from having synthesized the results of hundreds of clinical trials. The article from David Gunnell and colleagues, for example, at first appears particularly conclusive because, as an expert advisor to the MHRA, Gunnell had access to both published and unpublished clinical trial data. This enabled him to examine the use of SSRIs in over 40,000 individuals participating in 477 randomized controlled trials.

I met with Gunnell for an interview in June 2005. He was surprised when I told him that his *BMJ* article had been cited by people such as Nutt as proof that SSRIs do not lead to suicide. He stressed that, as he had clearly written in the article's conclusions, he felt the number of subjects in the trials had not been large enough to arbitrate on the safety of the drugs. Because suicide is a rare endpoint, larger trials are needed to arbitrate on the possibility of its occurrence – specifically, trials upwards of two million people. As he noted himself, the likelihood of such trials being carried out is rare:

In this case, we're talking about a trial to detect beneficial effect on suicide rates at around two million people. It would be very unusual to fund a trial in order to detect a harmful effect of a drug above a beneficial one. I think it's improbable that we're going to see trials in which two million people are randomized to antidepressants to look at the effectiveness of the drugs (LM interview with David Gunnell in June, 2005).

Gunnell also pointed out, in both the BMJ article and during our interview, a second factor that has made it hard to determine the efficacy and safety of SSRIs in comparison to placebo: that is the fact that there appears to have been underreporting by clinical trial investigators of the instances when subjects on the trials exhibited signs of self-harm. In examining the 477 trials, Gunnell looked for three endpoints:

1) The number of completed suicides, 2) the number of incidents of non-fatal self-harm, and 3) levels of suicidal ideation — instances where the trial volunteers reported feeling suicidal impulses or thoughts. An estimated total of 16 suicides, 172 episodes of non-fatal self harm, and 177 episodes of suicidal thoughts were reported, leading Gunnell and colleagues to conclude that, “Increased risks of suicide and self harm caused by SSRIs cannot be ruled out, but larger trials with longer follow up are required to assess the balance of risks and benefits fully” (Gunnell, Saperia et al. 2005).

What was particularly striking, as Gunnell noted both in the *BMJ* article and during our interview, was the ratio, in the trials, of completed suicides to reports of self-harm. In his meta-analysis of the SSRI trials, Gunnell found that the ratio of suicides to reported self-harm was 1:10. That ratio is significantly lower than the general population in England and Wales, where the ratio of completed suicides to incidence of self-harm is around 1:30 to 1:40.

Why would there be a far lower incident rate of self-harm among the populations enrolled in SSRI trials? Logically, given that this population represents individuals suffering from depression, one would expect them to emerge as *more* given to self-harm and suicidal thoughts than the average population, and not less. As this ratio of 1:10 was consistent for both the SSRI and the placebo arms of the trials, the lowered incidence of self-harm can not be attributed to the efficacy of SSRIs. One possible explanation could be that the therapeutic benefit of simply enrolling in the trial helped to lower rates of self-harm. Another possibility is that for some reason trials subjects did not report incidents of self-harm to investigators. A third possibility is that there was systematic underreporting by trial investigators, who did

not make a record of all the times when a patient indicated suicidal behaviour while the trials were being conducted. As Gunnell noted in the *BMJ*:

About 5000 suicides and over 142 000 episodes of non-fatal self harm occur each year in England and Wales, giving a ratio of roughly 1:30. As over-reporting of suicides is unlikely, the lower ratio in the trials in our meta-analysis is likely to reflect underreporting of episodes of self harm (Gunnell, Saperia et al. 2005).

Though Gunnell and his colleague raised the possibility of underreporting, the question remains as to whether it was deliberate or not. In our interview, Gunnell was reluctant to suggest there was deliberate misreporting of data:

DG: One of the challenges with these issues is that the trials are often conducted at a time when more widespread concern about self-harm, suicidal thoughts, suicide was just, I think, seen as being implausible in the eyes of the people who carried out these trials. And so the systematic recording of some of these end-points isn't as good as it might have been...

LM: ...A cynic would say that your interpretation of the idea that it was simply implausible of those designing the trials – a cynic would say that there was deliberate suppression.

DG: A cynic may say that. I'm not in a position to. I don't know. I really can't comment on that particular issue. I mean, if that was to occur, that's a big problem. You're entering into debates about the probity of the reporting and the conduct of research by organizations who stand to make a profit out of the sales of their drugs. And, it has been a concern that there's evidence to support that concern about suppression of information. It's appeared in the literature in the last few years. And I think that's very distressing. I think if the people's whose prime aim in life is to improve the public health; to sense that they're making...clinical guidelines and recommendations on less than perfect information, and if those aren't the right recommendations, then that's very worrying from the public health perspective.

Recently, some observers have suggested that the practice of distorting or underreporting endpoints may be widespread. An excerpt from my second interview with Tim Kendall provides an example. This excerpt focuses on how endpoints are presented when translated into published articles or conference posters.

TK: We have been able, at times, to identify some of the ways in which the drug industry makes selective use of evidence – distorts evidence in my view – in order to make claims that are in excess of the data. An excellent recent example of this is in the case of venlafaxine, [an antidepressant] made by Wyeth. Now, while we were undertaking the NICE guideline for the treatment

of depression in children, the National Collaborating Centre was also writing the guideline for depression in adults. Whilst we were working on this guideline, we became aware that Wyeth has sponsored an unpublished systematic review, by Thase and colleagues, which had been going around all the conferences as a poster. It contained a range of published and unpublished trials. On the basis of this it was claimed that venlafaxine was roughly 30% more effective than SSRIs. Wyeth sent us a summary of this review as 'stakeholder evidence'. We contacted Wyeth, who rather surprisingly sent us the review, and even some of the [independent patient] data that had gone into their meta-analysis. So, we had a look at their review, and we also, independently, undertook our own review, and then we compared the two results.

We found the Thase review presented data in quite an unusual way, which made it look as if venlafaxine was 30% better than SSRIs, when in fact it is not. What they had done was revealing. Firstly, they had used an odds ratio rather than a relative risk for comparing the effectiveness of venlafaxine and SSRIs in treating adult depression. The odds ratio of 1:30 suggested a 30% superiority for venlafaxine. A more appropriate statistical measure to use in this context is a relative risk ratio. So, using their unpublished trial data, we converted the odds ratios to a relative risk ratio. This gave us a figure of 0.9 relative risk; which suggests a 10% superiority for venlafaxine over the SSRIs. Secondly, the Thase review reversed the forest plot axes. Forest plots are a visual way of presenting meta-analytic data. The problem is that the forest plots are on a log scale, so if you reverse the axes, the effects look much better than they in fact are. This will matter if you are shown this data as a poster at a conference, where clinicians may not be aware of the subtleties involved, either in the statistical methods, or in the visual presentation of axes. It's a bit of a trick really, on their part.

A third important difference between the Thase review and our review relates to inclusion criteria. We couldn't tell which trials they included and which they excluded. We also couldn't discern the basis for inclusion and exclusion. Clearly, if you include mainly positive trials (and they included a number of positive unpublished trials that we couldn't get), then the review will be biased towards positive outcomes. It's important that you include *all* trials that are of good quality, irrespective of the outcome.

Finally, the Thase review makes no distinction between statistical and clinical significance. This is really a very common problem in all of medicine – not just in psychiatry. It's difficult to stress how widespread this problem is; clinicians and editors at medical journals often accept meta-analytic results without adequately scrutinizing whether any clinical significance has in fact been demonstrated. If you can show there is a statistically significant difference between a drug and placebo or a comparator, that's taken to mean the drug is better – even if the size of that difference is paltry.

You can seriously distort the evidence from systematic reviews through the tricks above. Reviews are very susceptible to manipulation. At any rate, although we could not get access to all the unpublished trial data, we were able to undo, step by step, the flaws in the Thase review, reforming it to meet NICE standards. Our final result indicated there was no statistically or clinically significant difference in efficacy between venlafaxine and SSRIs in adult depression (Kendall and McGoev 2007: 135-136).

Some have suggested that the inability of RCT evidence to arbitrate on things such as rare, yet lethal side-effects, calls for the need to challenge the emphasis placed on RCTs, over other forms of evidence, in licensing new medicines (Healy 2001). In the area of mental health, in particular, the reliance on rating scales such as the Hamilton Rating Scale for Depression, where subjective phenomena – feelings of self-worth, fatigue, stress – are translated into objective measurements via questionnaires – has led some to question the usefulness of RCT in determining both the benefits and risk of treatments. As Healy notes, “distinctions between treatment effects and effectiveness are a particular problem in the case of clinical trials in psychiatry, where the end-points of treatment are surrogate ones based on changes in rating scale scores rather than demonstrations of return to work, reduced mortality or absent bacterial loads” (Healy 2001: 323).

Another problem with the use of the rating scales is that, as Susan Bailey pointed out during our interview, often standardized scales are imported to a trial without adequate consideration of whether the measurements are appropriate for the age of the subjects in a trial. Bailey said that in examining SSRI trials in children, the MHRA did not take into account whether the measurement tools used in some of the studies were appropriate for a paediatric population. In some cases, three-year-old toddlers were given written questionnaires to read and respond to:

I did try and question the MHRA about the assessment tools they used in these trials, where they've got very young children. Because with very young children, you do not give them questionnaires. You give them picture questionnaires. Because, you cannot assess a fifteen year old in the same way as you would assess – if you can believe it, some kids as young as three had [written questionnaires]...But [the MHRA] were not won over to tell me what the assessment methods were.

Despite the many factors that leave RCTs open to manipulation by those who have something to gain by the demonstration of a particular effect, RCTs have attained a level of moral authority in medicine that elevates them above other forms

of experimentation. In the remainder of this chapter, drawing on work by Jack Goody and Maurice Bloch, I argue this authority of RCTs stems in part from the erroneous view of RCTs as abstracted from the political and commercial conditions of their production.

The social character of RCTs and the illusion of political flexibility

The anthropologist and social theorist Maurice Bloch has offered a critique of Goody's work on literacy which is relevant to an analysis of the political and social uses of RCTs. According to Goody, knowledge in pre-literate societies remained buried in social relations. With the introduction of literacy, however, political authority may be challenged, and science – now separate from the social relations in which it was produced – is better able to flourish and develop. Literacy “made it possible to scrutinise discourse in a different kind by giving oral communication a semi-permanent form; the scrutiny favoured the increase in the scope of critical active, and hence of rationality, scepticism, and logic” (Goody 1977: 37).

Bloch offers an extended ethnographic example in order to rebuke Goody's argument, and to assert in contrast that, though literacy may seem to make certain types of knowledge more accessible, it does not remove the socio-economic constraints on accessing and employing different forms of knowledge. Bloch draws on the example of a conference he attended in Madagascar in 1984, at which participants consisted mostly of Malagasy historians and students, as well as some foreign scholars such as Bloch. Also in attendance were a few “local worthies”: distinguished local magistrates, a few heads of large businesses, and most prominently of all, a local historian and politician named Arthur Besy. Besy's area of expertise dealt with the history of his personal native region of Tamatave, the topic

on which he chose to speak at the conference. Though all other attendees had been allocated only 15 minutes to speak to their papers, Besy gave an oratorical address lasting over two hours – in the most eloquent and traditional Malagasy, which other speakers had avoided in politeness to the non-Malagasy speakers present. Though as an academic historical account, the paper was unconvincing to his colleagues, they nonetheless “listened respectfully, if not perhaps very attentively, to this grand, oratorical performance” (1998: 155).

Besy himself, Bloch notes, took the attention in hand as though as it was no more than simply his proper due: “Indeed, he delicately implied that young upstarts like the people from the university or myself, although we were doing something which he could understand had its own rationale and rigour, and which had a place within its own limited and rather unimportant context, was not really history” (156). In giving his talk in traditional Malagasy, Besy was partly exploiting a distinction between two kinds of language uses which is fundamental to Merina culture. On the one hand there is ordinary talk which is marked by informal style; on the other, a formal form of oration known as *Kabary*. The distinction between language use, Bloch notes, was widely incorporated and employed into written language once literacy grew more widespread in Madagascar. This adoption of the distinction by the Malagasy helps to explain the “irrelevance of literacy as an ideological transforming agent in this case.” The written word is largely seen, Bloch notes,

as a form of ancestral oratory. As a result it is largely treated in similar ways as oral *Kabary*. People without authority have no right to use it, and if they do, they are ridiculous... Written documents are not, any more than the words of a respected elder who uses the style of ancestral oratory, open to critical examination and evaluation... Literacy did not act on its own, rather people used literacy for their own purposes. The people who were using literacy were part of a system of social relations and therefore it was in terms of that system of social relations that literacy was significant and its relation to knowledge was in terms of these uses. Literacy did not desocialize knowledge as is implied by Goody and it therefore had no political significance as a democratizing agent” (1998: 160-161).

Bloch's point – that literacy alone does not desocialize knowledge from the origins of its production – is relevant to the question of why, against the hopes and aims of those who espouse the merits of RCTs, the introduction of their use to medical practice has not fostered the democratic levelling of relations between clinicians and patients that was once proclaimed. Nor has it fostered, as Fisher once hoped, the ability of “thinking men” to scrutinize the authority of statisticians, clinicians or political authorities. As this chapter has illustrated, attempts to scrutinize the data of SSRIs has led only to the realization that, firstly, the data on the safety of SSRIs was lacking clarity, and secondly, that practitioners had very little authority to elicit the data that could help clarify debates. From Kendall's frustrated efforts to have the MHRA tell practitioners what proportion of trials had been made public, to Bailey's request for the assessment criteria used in SSRI trials, the theme that has most clearly emerged is the *inability* of individuals to access the very evidence that has purportedly, ever since the advent of EBM, become more freely available at places like the Cochrane Collaboration.

In the essay “What's in a list?”, Goody, noting that the word ‘list’ is “one of those polysemic words in which English abounds,” offers the following definition of the seemingly simple word:

The O.E.D. gives (lists) seven substantive usages, relating to listening and lusting, etc. The third has to do with the ‘border, edging, strip, selvage of a cloth.’ Closely associated with this meaning is that of a boundary, for example, ‘a place within which a combat takes place.’; hence ‘to enter the lists’ means to go in to the area marked for combat (1977: 80).

Though his aim is largely to call attention to etymology of the word, Goody inadvertently returns us to Latour's crucial point on the agonistic starting-point from which one should approach inscriptions and immutable mobiles. Latour invokes the

literalness of the battles over inscriptions; he returns our attention to the observation that “‘paper shuffling’ is the source of an essential power, that constantly escapes attention since its materiality is ignored” (1986: 28). With this agonistic point in mind, it is possible to ask both “what’s in an RCT?”, as well as to examine who stands to gain the most from their construction, storage and dissemination – who derives the most power, in short, from their ‘paper shuffling’?

“The role of the bureaucrat,” Latour writes in the essay *Visualization and cognition*, “is always misunderstood because we take for granted that there exist, somewhere in society, macro-actors that naturally dominate the scene: Corporation, State, Productive Forces, Cultures, Imperialism.” Rather than such entities being the key, Latour argues, to understanding science and technology, it is things such as *corporation, state, and production* that a new understanding of science and technology can help to explain. In particular, an understanding of the simple authority encapsulated within the collection, storage, dissemination (or harbouring) of inscriptions can help to explain not simply the bureaucrat’s authority, but that of the macro-actors such as the corporation or the state thought to dominate the bureaucrats themselves:

A man is never much more powerful than any other – even from a throne; but a man whose eyes dominate records through which some sort of connection are established with millions of others may be said to *dominate* (29).

Latour’s point lets us see that RCTs do represent a form of authority – but not the democratising or empowering authority first envisioned of them by EBM proponents. Instead, RCTs – and their guardians in places such as the MHRA or the marketing departments of pharmaceutical companies – have emerged as a remarkably *anti-political* phenomena, anti-political in that they diminish, rather than augment, the space for contestation, challenge and debate.

Scholars such as Foucault, Hacking and Rose have long drawn our attention to the reliance on statistical surveys as bulwarks of governmental authority: “Statistics, in enabling the taming of chance, in turning a qualitative world into information and rendering it amenable to control, in establishing the classifications by which people come to think of themselves and their choices, appears to be bound up with an apparatus of domination” (Rose 1999: 203).

RCTs, as Rose has noted of the function of numbers in general, serve to depoliticize areas of political decision-making “by purporting to act as automatic, technical mechanisms for making judgments”(1999: 198). It is the very illusion of objectivity, the seeming neutrality of numbers, that renders opposition difficult unless it is phrased in the language of the very methods one seeks to oppose.

This relates to work by Barry, who has proposed a distinction between “politics,” which he terms a “set of technical practices, forms of knowledge and institutions,” and the “political,” which he views as a barometer, or an index, of the space available for disagreement and contestation (Barry 2002: 268). In this light, an action can be viewed as political to the extent that it creates room and openings for the possibility for disagreement. Technical discussions, scientific deliberations, the minutia of debates over quantifiable measurements – phenomena which are regularly drawn on in political debates, can be seen as *anti-political*, in that they have the effect of closing the space for disagreement to those who have the expertise and scientific capital to involve themselves in technical decisions. As Barry notes:

Seen in these terms what is commonly termed politics is not necessarily – or generally – political in its consequences. Politics can often be profoundly anti-politic in its effects: suppressing potential spaces of contestation; placing limits on the possibilities for debate and confrontation. Indeed, one might say that one of the core functions of politics has been, and should be, to place limits on the political (Barry 2002: 270).

Barry's argument helps to illuminate what I have stressed throughout this thesis. Contrary to the view that medicine is "all about politics," as some complained to me during the SSRI controversy, I have suggested that medicine is increasingly *anti-political*, in the sense of there being an ever-diminishing scope for contestation and debate.

At first glance, the very willingness of practitioners to speak with me – often voicing political criticisms of the regulatory handling of the SSRI controversy – indicates a weakness of my argument. How could it be true that the rise of EBM has curbed the ability of individual clinicians to critique medical practices, given the very positive response rate to my requests for interviews? Clinicians, particularly in the wake of recent debates over the safety of a number of pharmaceuticals, from Prozac to Vioxx, seem on the whole more politicized than they have been in recent decades.

I am not suggesting, however, that the *desire* to engage professionally, to critique one's profession, to scrutinize the delivery of services, has weakened. Only that, in order to justify one's criticism and gain an audience for one's objections, a dissenting argument must be defended through recourse to RCT evidence. In other words, one must have the cultural and professional capital to gain access to the very data and methodology one often finds problematic.

A second possible criticism of my argument is that evidence-based medicine, by leading to the development of bodies such as the Cochrane which make clinical trial information available with the click of a mouse, has obviously rendered clinical trial data more accessible – thus *arming* individuals with the tools they need to object to a dominant view on the safety of a given treatment.

Such an observation, however, ignores one of the most paradoxical implications of the emergence of EBM, which is that while some information is

rendered more accessible at places such as Cochrane, the retention of a legal framework disposed to commercial confidentiality rights, and the increasing development of industry funded regulators, leads to bifurcated evidence bases. On the one hand, as a result of bodies such as Medline, PubMed and Cochrane, there is an abundance of information in the public domain. On the other hand, very few individuals have a legal right to the full evidence base on a given treatment, casting doubt over the reliability of the data that is available.

Related to this, it is the very *illusion* of greater access to trial data that makes it harder to appreciate how much information remains legally impossible to obtain. The perception of having more access to clinical trial data as a result of bodies such as Cochrane has made it harder to grasp the ways that the rise of EBM has limited the ability of clinicians and patients to contest authoritative statements on a treatment's safety and efficacy. Clinicians are limited by the very appearance of having more opportunity.

Conclusions

In this chapter, I have suggested RCTs are a form of inscriptions, the authority of which consists of rendering information mobile and immutable, and seemingly detached from the authority of those who have produced the inscriptions. To return to a quote from the previous chapter, Kaptchuk has suggested that, "the aura of objectivity and neutrality attached to blind assessment itself may have benefited from this absence of a past" (Kaptchuk 1998: 390). Similarly, the authority of RCTs stems in part from the illusionary view of RCT evidence as uninfluenced by the political and social relations in which they are produced.

This authority is not, however, impervious to challenge. Although RCTs have emerged as an anti-political phenomena, narrowing the room for debate and dissent by fostering an illusion of scientific certainty, a key strategy of those seeking to contest the authority of a given RCT has been to point out how industry practices, such as withholding negative trial data, can render the evidence from RCTs uncertain and unreliable (Roberts, Li Wan Po et al. 1998).

This has been the tactic employed by people such as Bailey, Kendall and Shooter, who have argued that the industry's withholding of SSRI data, such as the refusal to supply unpublished trials when Kendall's team at NCCMH was first formulating the NICE guidelines for paediatric medicine, led to the perception of SSRIs as more efficacious than they were shown to be once unpublished trials were included in meta-analyses. It seems apparent that if the certainty commanded by RCTs closes the space for disagreement and dissent, a solution for those wishing to have a voice in disagreements over drug safety is to find a way to cast doubt on the technical certitude of policy decisions. As logical, however, as this seems, in practice one typically requires technical expertise in order to cast doubt on the technical conclusions of others. In the next chapter, I address this paradox by exploring the value of uncertainty in debates over the safety of drugs, assessing for whom, and under what institutional constraints, uncertainty can serve as a form of capital.

Chapter 7: The Consolations of Chaos: The performative nature of uncertainty

To know and not to know, to be conscious of complete truthfulness while telling carefully constructed lies, to hold simultaneously two opinions which cancelled out, knowing them to be contradictory and believing in both of them...to forget whatever it was necessary to forget, then to draw it back into memory again at the moment when it was needed, and then promptly to forget it again: and above all, to apply the same process to the process itself. That was the ultimate subtlety (George Orwell, 1984).

Introduction

In this chapter, I explore the value of uncertainty in drug regulation through an empirical focus on the legal difficulties in accessing unpublished clinical trial data held by manufacturers and industry. The structure of the chapter is as follows. Firstly, drawing on the example of Vioxx, I argue the suppression and distortion of trial data is not restricted to the SSRIs, but is discernable across the pharmaceutical industry. Extrapolating from the example of Vioxx, I then explore what I view as the performative value of uncertainty: the way uncertainty creates a need for resolution to the ambiguity which it perpetuates. Thirdly, I draw parallels between the SSRI and Vioxx controversies and the case of Enron, where executives at the now defunct energy company misrepresented Enron's financial status in statements submitted to regulators, as well as carrying out other fraudulent acts. Fourthly, I explore proposals to ameliorate problems surrounding the disclosure of clinical trials, such as the recent call for a "Sarbanes Oxley for Science," a reference to the US securities legislation passed in the wake of the Enron and Worldcom scandals. Finally, I return to the case of SSRIs in order to explore something rarely discussed in debates over access to

clinical trial data: the fact that, regardless of how much data is disclosed by drug manufacturers, regulators often face a number of institutional constraints in acting on the data that is provided to them. This finding illuminates a number of weaknesses within calls for more “transparency” in the pharmaceutical industry.

Shifting the evidence: Truth, disclosure and the usefulness of conflicting facts

The question of whether pharmaceutical companies and academic researchers should be legally forced to disclose the results of clinical trials where a product appears in a negative light has been surprisingly underappreciated in medicine and healthcare delivery. Despite the fact that some practitioners have been calling attention to the problem for years, only very recently, partly as a result of the high-profile controversies over Prozac and Vioxx, has the problem received much public attention. As Chalmers wrote to me in an email in October 2006, the “problem of publication bias was recognized by some of us long before the Cochrane Collaboration existed, yet people didn’t listen to us. I tried to get ministers interested, but with no success...it really wasn’t until Eliot Spitzer challenged GSK [over the withholding of SSRI data] that anything serious happened” (October 2006).¹⁵

If there have been any positive consequences of the debates over SSRIs, it is that policymakers have become more aware of how limited access to trial data can affect treatment options and decisions. In the last few years, policymakers have joined with scientists and practitioners such as Chalmers in insisting that companies should make clinical trial data public. Their efforts, as I noted in Chapter Two, have led to the establishment of national and international clinical trials registries where

¹⁵ Personal email, quoted with permission.

companies are expected to post trial information (Rennie 2004). Because of their voluntary nature, however, there is very little enforcement in place to ensure companies comply with the onus to disclose trials. In the UK, for example, as Kendall noted to me, despite the Labour government stating in their last election manifesto that they will legally force drug companies to publish trials, it “has not become mandatory in any meaningful way” (Kendall and McGoey 2007: 137).

Somewhat more optimistically, major medical journals such as the *British Medical Journal*, *Lancet* and the *Journal of the American Medical Association (JAMA)* are taking action themselves, insisting they will not publish a trial unless it has been registered prior to its commencement. Also, some journals such as *JAMA* are refusing to publish a study unless the trial’s investigators are willing to allow an external, independent group access to a study’s individual patient-level data (Kendall and McGoey 2007).

Despite these very recent developments, the problem of access to data remains underappreciated. One reason why is that, aside from efforts by medical journals to police the studies reported in medical literature, there have been very few punitive consequences for companies that are widely suspected to have withheld clinical trial data pertinent to drugs such as Vioxx and SSRIs. Some observers equate the lack of punitive measures as evidence that companies have not acted as egregiously as the media have suggested. What they fail to consider is that the absence of legal reprimands is not necessarily proof of a company’s innocence, but may simply illuminate a regulatory or judicial body’s inefficiency at prosecuting malfeasance.

In this chapter, I explore three outstanding questions surrounding the disclosure of clinical trials. First, the question of whether companies generally comply or not with the legal obligation to disclose all clinical trial data pertinent to a licence

application to UK regulators. Second, whether government regulators, for a variety of reasons, have failed to effectively monitor and prosecute the failure to disclose trial data. And third, whether companies should, in addition to submitting all data to regulators, make their findings universally accessible through posting data on public clinical trial registries. At first glance, these three factors seem related and complementary. It seems obvious that enforcing one aspect above, such as insisting that companies disclose all findings to regulators, would expedite positive outcomes in the second two areas. In practice, I suggest, the opposite is the case. The factors above – increasing regulatory access to data, increasingly the regulatory ability to enforce breaches of disclosure, and increasing public access – are often incommensurate and incompatible. In practice, efforts to strengthen disclosure in one area often create a need for more obscurity in others.

For example, in order for the MHRA to remain regionally competitive among EU regulators vying for licensing fees from industry, MHRA regulators have an interest in maintaining a favourable relationship with the companies funding their operations. Arguably, increasing public access to trials is not in the interest of regulators whose institutional survival is contingent on maintaining a position of regulatory exclusivity.

Barry, drawing on Simmel's classic work on secrecy, has stressed the dialogical character of secrecy and transparency, the way "transparency, as George Simmel recognized, is associated with discretion. If transparency involves a commitment to make things public, then it is necessary to not investigate or know about matters if they are not to become public. Discretion involves more or less deliberate non-knowledge" (Barry 2006: 3-4; Barry 2006).

With the exception of this insight, it is remarkable how often observers have neglected or misperceived the interrelated nature of secrecy and disclosure. As a result of this neglect, observers are able to suggest, as most do when observing the recent series of high-profile controversies of adverse drug effects, that the answer to such catastrophes is simply more transparency. In reality, the demand for more transparency often creates a parallel need for more creative strategies of non-disclosure and evasion. At times, these strategies have a more intractable and imperceptible character than the initial strategies of evasion which provoked calls for more transparency in the first place. A strategy of “factual ignorance” can be harder to detect than a strategy of secrecy.¹⁶

The disclosure of clinical trials to the MHRA

As noted in Chapter Four, medicines legislation in the UK and EU stipulates that any pharmaceutical company seeking a licence must give regulators all clinical trial data that has a bearing on the risk and benefit profile of a drug (Jackson 2006; Abraham 2007). During his testimony before the UK Health Select Committee’s inquiry into the influence of the pharmaceutical industry, Woods stressed this point:

Q38: Siabhain McDonagh: How many clinical trials does the MHRA examine before approving a drug application? Is the MHRA confident that it completely reviews all the findings necessary, both within and outside the public domain, before licensing a drug?

Professor Woods: The legal responsibility is on the applicant to ensure that in applying for a trial’s authorisation they do give us all the data, whether or not it is in the public domain. That is clearly spelt out in the medicines legislation, and, of course, it is fundamental to our assessment of a product that we do have access to all the available data...if we have evidence that there has been a breach of the regulations, then we have an inspection and enforcement divisions

¹⁶ Recently, literature in regulation studies has started to scrutinize the interrelated nature of secrecy and transparency, as well to question the belief that explicit transparency always render a phenomenon more visible or actionable. In some cases, as contributions to Christopher Hood and David Heald’s recent edited volume on transparency point out, transparency can serve as a guise for more secrecy (2006). Work by political theorist Jacqueline Best also supports this point (2007).

which will take the necessary action to pursue investigations...we have had occasion to involve our enforcement group where there has been some evidence to suggest that we have not been given data at the appropriate point (HOCa 2005: 25).

Once an MHRA investigation into a possible breach of the Medicines Act is complete, “the evidence is then passed to government prosecutors, whose job it is to decide whether the evidence supports a prosecution. For the MHRA, this is usually done by solicitors employed by the Department of Work and Pensions, drawing on the expertise of barristers as needed” (MHRA 2007). If found guilty, penalties include imprisonment or fines (Durman and Rushe 2004). To date in the UK – as Woods confirmed to me during our interview – no company has even been prosecuted for withholding clinical trial information that has a bearing on a drug’s safety profile.¹⁷ Given that, as Woods notes in the excerpt above, companies have on occasion faced inspections for the suspected failure to submit data, the fact that no company has ever been prosecuted suggests that a) suspicions were incorrect, and no company has to date ever withheld problematic data; b) the MHRA failed to effectively detect such behaviour; or c) the Department of Work and Pensions, the prosecuting authority, chose not to act on MHRA recommendations.

In the following section, I broaden the focus away from SSRIs in order to argue that point “a” above, the idea that companies have unfailingly provided all necessary information to regulators, is not plausible. In fact, the converse seems the case. Drawing on the recent example of Merck’s Vioxx, the anti-inflammatory drug removed from the US market in 2004, as well as work by sociologists such as John

¹⁷ Among UK regulatory agencies, low rates of prosecution for lack of compliance are not unusual. As Keith Hawkins notes, legal measures are seen as a “last resort,” particularly as “the use of law seems to be regarded by regulatory officials in Britain as a rather hazardous enterprise, posing risks of failure to both the individual and his or her organization” (Hawkins 1989: 371; Hawkins 2002). The fact that prosecutions are rare does not undermine their importance: Their rarity itself, as Hawkins notes, is worthy of sociological attention.

Braithwaite, I suggest that the withholding of clinical trial data is common practice among pharmaceutical companies.

Further, I argue there are parallels between the allegations of clinical trial fraud at GlaxoSmithKline and Merck, and the distortion of financial certificates at companies such as Enron. In the cases of GSK, Merck and Enron, questions have turned on whether companies were sufficiently forthcoming in their submissions to regulators such as the FDA, MHRA and the Securities Exchange Commission (SEC) (c.f. Heminway 2003; Lancet 2004). In all cases, the scrutiny of problematic behaviour has been hampered by the financial structure of regulatory and auditing bodies, and the fact that the parties mandated with detecting fraud are financially dependent on the companies they are investigating, something well-documented in literature on regulatory capture (c.f. Macey 2003). A second deterrent to the detection of fraud has been the common view among policymakers and economists that, as it is not believed to be in a company's economic self-interest to commit fraudulent acts, it was initially unthinkable that levels of fraud could have climbed to the heights which they did in the Enron case.

A final parallel between controversies over the manipulation of trial data and controversies over the manipulation of financial statements has been the shared *response*, among members of the public, interest groups, and government authorities, to the suggestion that fraud has been committed. That response has generally been two-fold. First, authorities have demanded greater public disclosure, transparency and accountability. Secondly, policy advisors have sought to strengthen the regulatory apparatuses that failed to detect fraud expediently in the past. Little attention is paid to the way the second response – efforts to strengthen regulatory

apparatuses – can work in practice to prevent the realization of the first goal: creating more transparency.

Pharmaceutical scandals: Vioxx, and the regulatory usefulness of conflicting facts

In the following sections, I provide an analysis of the recent controversy over Vioxx, the anti-inflammatory manufactured by Merck. Throughout this thesis, I have focused on the UK response to questions over SSRIs. In the case of Vioxx, I focus on the United States and the FDA. My intent here is to illustrate that problems surrounding the MHRA's handling of SSRIs are not unique to the UK. Regulators on both sides of the Atlantic are subject to a number of pressures which hinder effective drugs regulation. Also, by broadening the geographical and national focus, I seek to stress my argument that, contrary to the view that it is not in a company's economic interest to suppress trial data, such behaviour may be useful for industry.

In the last few years, a number of books, many of them written by leading health scholars, such as Marcia Angell, former editor of the *New England Journal of Medicine*, have sought to “expose” the corruption and malfeasance in the pharmaceutical industry (Relman and Angell 1992; Angell 2004). A weakness of these books is their revelatory tone. In reality, there is nothing novel about the suggestion that the pharmaceutical industry routinely engages in fraudulent acts. John Braithwaite's *Corporate Crime in the Pharmaceutical Industry* (Braithwaite 1984) detailed a litany of illegal actions regularly conducted by top companies such as monopolistic behaviour, “drug dumping” unsafe substances in developing regions, bribing regulatory officials, and the manipulation of clinical trials data. Braithwaite's book was feted in top scholarly journals, such as *Organization Studies*, where an article declared “thank goodness for Mother Jones, The Wall Street Journal, the

Securities and Exchange Commission, Senate Sub-Committees, the Food and Drug Administration, the Sunday Times Insight Team and John Braithwaite. All, in some way, have highlighted the malpractices of the multinationals and/or have exposed the nefarious side of the drug companies” (Punch 1986: 92)

If there is little new about allegations of corruption inside companies, certainly the external challenges faced by pharmaceutical firms have changed in a number of ways. One of the developments in the twenty years between Braithwaite and Angell’s books has been the emergence of the Internet, which has led to the growth of grassroots networks where consumers circulate evidence of adverse effects, and post personal stories on websites such as www.globalserialkillers.com, an acrimonious spoof of GSK. In the case of both the SSRIs and Vioxx, it was in part consumer reports of adverse effects that forced regulators to continually reassess the drugs, even when, as the case below of Vioxx indicates, some regulators did not wish to call attention to the possibility of earlier regulatory mistakes.

Profitable failure: the case of Vioxx

Vioxx, for which the chemical name is rofecoxib, is a COX-2 inhibitor introduced in 1999 as a safer, more effective alternative to non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain associated with osteoarthritis. As a result of evidence linking the drug to cardiovascular failure in some users, the drug was removed from the US market on September 30, 2004 – a day which Harvard University physician Jerry Avorn recently suggested is “fast becoming a day of infamy for drug safety” (Avorn 2003: 2169). Prior to its removal from the US market, nearly 107 million prescriptions had been dispensed in the US (Krumholz, Ross et al. 2007, quoting IMS health data), and annual sales had

surpassed \$2.5 billion (US). Its removal represents, as US cardiologist Eric Topol notes in the *New England Journal of Medicine*, the largest prescription drug withdrawal in history (Topol 2004).

When Merck first pulled Vioxx from the market, many observers praised the company's willingness to admit the risks of its own product. As *Lancet* editor Richard Horton suggested, "For Merck to act so promptly in the face of these most recent safety concerns is commendable and should serve as an example of responsible pharmaceutical practice" (Horton 2004: 1287). One month later, Horton retracted the comments, noting "our praise was premature" (Horton 2004). On December 4, 2004 the *Lancet* published a meta-analysis (Juni, Nartey et al. 2004) which revealed that "unacceptable cardiovascular risks" were evident as early as 2000 (Horton 2004: 1995). Meanwhile, investigations by journalists at the *Wall Street Journal* revealed a series of e-mails confirming that Merck executives were aware of the adverse effects of Vioxx at least as early as 2000. One marketing document addressed to sales representatives referred to the drug as "Dodge Ball Vioxx" in discussing the best ways to placate the concerns of physicians who asked questions about the drug's safety (Horton 2004; Mathews and Martinez 2004).

The documents uncovered by the media were predicted to be the tip of Merck's economic downfall. An article in the *New York Times* suggested the Vioxx fallout would determine "whether Merck will survive as a strong, independent company or will be crippled for years to come" (Berenson 2005). "The pain is just beginning," reported a *BusinessWeek* article in September 2005, suggesting the Vioxx debacle might cripple Merck irrevocably: "Merck & Co. now looks likely to emerge from its Vioxx mess as a weakened version of its former self: a second-tier player among its rivals" (BusinessWeek 2005).

Three years later these predictions have not materialized. A 2007 article in the *Financial Times* noted that “Recent drug sector darling Merck won accolades this week for boosting quarterly profits above Wall Street’s already-high expectations...Merck’s shares have doubled over the past two years” (FT 2007). “Fitter Merck looks ready to run,” reported an online commentary from Barron’s, the US investment bible, on October 29, 2007.

In the section below, I suggest that scientific uncertainty surrounding the risks and benefits of Vioxx has been integral to Merck’s ability to absolve its liability during the Vioxx controversy, contributing to its economic growth. In at least three ways, Merck has benefited from value of uncertainty: 1) They fomented scientific uncertainty by refusing to fund research that might have produced more conclusive evidence on the risks of Vioxx (see Berenson, Harris et al. 2004); 2) they did not include evidence of known adverse effects in articles submitted to journal editors (Curfman, Morrissey et al. 2005), and 3) they harnessed the uncertain nature of science itself – such as the difficulty in proving causation in drug-related injuries – as a legal strategy (see Culp and Berry 2007).

During 1999-2000, Merck carried out a randomized controlled trial known as the Vigor study, undertaken in order to help expand Vioxx’s FDA licence by demonstrating the drug carried fewer gastrointestinal side-effects than naproxen, a popular anti-inflammatory first licensed in the 1970s (Krumholz, Ross et al. 2007: 121). Although an early safety analysis from the clinical trial, presented to Merck’s safety board in 1999, revealed a 80% greater risk of death or serious cardiovascular event in the treatment group, the safety board allowed the study to continue until the drug’s effect in minimizing gastrointestinal side-effects could be determined. The final study did determine that Vioxx was effective in diminishing gastrointestinal

events. It also revealed, however, a significant increased risk of myocardial infarction on rofecoxib (Vioxx) over naproxen, something Merck's chief scientist Edward Scolnick referred to in an internal email as "a shame" (Krumholz, Ross et al. 2007: 121).¹⁸

Because the Vigor study was a comparison between two biologically active agents – naproxen and rofecoxib – Merck's scientists had a choice in how to interpret the results and to present their endpoint analysis for publication. They could either interpret the endpoints as indicating that rofecoxib increased the risk of heart attacks, or they could suggest that naproxen was actually a protective agent – decreasing the risk of myocardial infarction. The company chose the latter option, publishing the trial's results in an article in the *New England Journal of Medicine (NEJM)* (Bombardier, Laine et al. 2000) which suggested naproxen was cardioprotective – despite the fact there was no accepted evidence suggesting Naproxen reduced the risk of heart attacks (see Jasanoff 2006; Michaels 2006; Krumholz, Ross et al. 2007).

As Michaels notes:

It is hard to imagine that the company's scientists were deliberately promoting a drug they knew was unsafe. At the same time, it is hard to imagine they honestly thought naproxen reduced the risk of heart attack by 80 percent (Michaels 2005: 100).

Equally surprising is that the *NEJM* published the results of the Vigor study without initially questioning the suggestion of naproxen's protective properties. Since then, the *NEJM* has published a number of articles accusing Merck of withholding vital information from the journal's editorial board, leading to misleading conclusions on Vioxx's safety (Curfman, Morrissey et al. 2005).

¹⁸ In line with the majority of academic observers, I have tended to take a critical view of Merck's actions throughout the Vioxx controversy. For a more sympathetic description of the company's behaviour, see Lofstedt 2007.

The Vigor study was not the first time evidence arose of Vioxx's possible risks: A 1998 Merck clinical trial called "Study 090" showed that heart attack and stroke occurred almost six times more often in patient taken Vioxx than those on placebo or another arthritis drug. Merck chose not to disclose the study, claiming the study was too small to prove statistical significance (Culp and Berry 2007).

During testimony for Vioxx lawsuit, Raymond Gilmartin, Merck's former CEO, said that he never consciously masked safety data. When asked during cross-examination why Merck did not disclose the results of a 2000 internal analysis that indicated Vioxx carried a five-fold higher risk of heart attack over other pain relievers, Gilmartin noted that legally Merck was not obligated to turn over the analysis, as it was a preliminary study, not a completed clinical trial.

Lanier asked, "[a]re you saying it was important enough for Merck to do this study, but not important enough to send to the FDA?" No, I'm not telling you that at all," Gilmartin replied, stating that Merck's analysis was *only preliminary and thus potentially flawed* (Culp and Berry 2007: 16, emphasis added).

Gilmartin's comment suggests that the reticence to disclose an early study to the FDA stemmed from *caution*, and not deliberate deception. A theme emerges: time and again, Merck executives have returned to the uncertain nature of their own studies as justification for inaction.

An additional accusation is that Merck aggressively promoted Vioxx to physicians, advising sales representatives to stay silent on the question of the drug's safety when concerns were raised. In February 2001, for example, the FDA's Arthritis Drugs Advisory Committee met to discuss the Vigor study. Following the meeting, the advisory committee voted that physicians should be made aware of the possibility that Vioxx increased cardiovascular risks. The next day, Merck circulated a bulletin to sales representatives directing them *not* to raise the conclusions of the

FDA's Arthritis Advisory Committee with physicians, and stipulating that if a doctor asked about Vioxx, "the sales representative should indicate that the study showed a gastrointestinal benefit and then say, 'I cannot discuss this study with you'" (Waxman 2005).

Merck's tactics throughout the development and marketing of Vioxx have led to more than 27,000 civil suits (FDA 2007), including a suit from the Texas Attorney General. Among US federal agencies, the Justice Department has launched a criminal investigation into Merck's research, marketing and selling of Vioxx, and the Securities and Exchange Commission is conducting an inquiry (Culp and Berry 2007).

As David Culp and Isobel Berry describe, Merck's legal strategy has been two-fold: first, that they acted responsibly in voluntarily pulling Vioxx when irrefutable scientific evidence arose of cardiovascular risks; and second, that it is impossible to determine that Vioxx, and not confounding factors such as obesity, blood pressure or clogged arteries, led to an individual's death. This second strategy is a notorious one in lawsuits involving pharmaceutical drugs. As noted with SSRIs, because individuals taking medication are already ill, it is hard to determine whether the drug, or the underlying illness the drug is intended to treat, led to deteriorating health levels (Jackson 2006).

In November 2007, in a reversal of its earlier insistence that it would fight each legal case separately, Merck announced it would pay a settlement of \$4.85 billion for the approximately 45,000 plaintiffs represented in the 27,000 lawsuits. The cost was far less than earlier estimates of Merck's legal costs, which some predicted might be as high as \$30 billion (Tansey 2007). Merck's stock rose 2.1% on the news of the settlement, reaching levels (approximately \$58 in the days following the

announcement) that surpassed Merck's share value in the months preceding the withdrawal of Vioxx (approximately \$45).¹⁹ Although a number of factors have contributed to Merck's current financial strength, including a strong pipeline of drugs in development, one factor is that legal costs have not been as damaging as initially predicted. The uncertainty surrounding the many factors contributing to an individual's death – poor health, the uncertainty of a drug's mechanistic action, and the ambiguous nature of comorbidity (the presence of additional disorders in addition to a primary one) – has been legal manna for Merck executives.

Complicity of the FDA: reputational versus primary risk

Numerous parties involved with the Vioxx case, including the FDA, and, as noted earlier, the *NEJM* for first publishing the Vigor study, have been criticized for failing to detect the adverse effects of the drug. The most vocal critic inside the FDA has been David Graham, an associate director for science and medicine in the then-named Office of Drug Safety, a bureau within the agency's Center for Drug Evaluation and Research.

In the fall of 2004, Graham gave testimony before a US Senate Finance Committee investigation into the background of the withdrawal of Vioxx. During the hearing, Graham argued that, based on estimates drawn from risk levels visible in the two main Merck-sponsored RCTs, it is likely that 88,000 to 139,000 Americans suffered heart attacks as a result of Vioxx. Of those, it is likely that 30% to 40% died. Graham suggested that his FDA superiors not only refused to acknowledge the adverse effects of Vioxx, some of them launched a campaign of intimidation against whistle-blowers who sought to disclose concerns with the drug (Graham 2004).

¹⁹ Stock quotes taken from www.moneycentral.msn.com, last accessed November 2007.

Graham noted that he had first become concerned about the risks of Vioxx in 2000 following the publication of the VIGOR study. His concerns led him to work with Kaiser Permanente, a US health management organization, in performing an epidemiological study involving 1.4 million of Kaiser Permanente patients given either Vioxx or one of its competitors, Celebrex. Based on this data, Graham suggested in a presentation given during the summer of 2004 that 27,000 heart attacks and sudden cardiac deaths might have been avoided if the patients had used Celebrex rather than Vioxx (Kaufmann 2004).

The presentation prompted a letter from the FDA's Office of New Drugs, who said that because the FDA was not considering a warning against the use of Vioxx, Graham should change his conclusions on the drug. At a meeting on September 22, Graham was asked by superiors why he had felt the need to study Vioxx when the FDA had already made its labelling decisions and therefore no further scrutiny was required. Eight days following this meeting, Graham's concerns were reinforced by Merck's decision to voluntarily pull Vioxx from the US market.

In his Senate testimony, Graham said his experience with Vioxx was typical of how the FDA's Center for Drug Evaluation and Research responded to drug safety issues in general, and drew parallels to the treatment of Andrew Mosholder, an FDA scientist whose investigation into the suicide risks of SSRIs in children was allegedly suppressed by the FDA (Lenzer 2004; Jasanoff 2006). Graham added the following comment:

I could bore you with a long list of prominent and not-so-prominent safety issues where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it *called into question an existent regulatory position*. In these situations, the [office] that approved the drug in the first place...typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues (Graham 2004: 3, emphasis added).

Graham's comment reflects the point I made in Chapter Three, where I supported that concerns over drawing attention to their own earlier mistakes prevented MHRA regulators from acting on the knowledge of the adverse effects of SSRIs when they first learned of them. This argument is supported by work from Power, who has stressed that, in an increasingly litigious and compensatory culture, an organization's need to address reputational risks is increasingly superseding the need to address the primary risks which an organization is mandated to avert (Power 2004).

On the other hand, the failure to address primary risks has obvious consequences for one's reputation. Therefore if only to protect one's reputation, it seems apparent that it is in the interest of a regulator, or any organization, to conduct its business competently and lawfully. As logical as this may be, often numerous institutional pressures hinder the ability of an organization or an individual from acting in the most seemingly advantageous or rational way. In the case above of the FDA, for example, individuals were beholden to intra-agency boundary disputes and rivalries (c.f. Gieryn 1999) which stymied the desire or the ability to act on Graham's findings. If, therefore, one is unable to address primary risks, regardless of how advantageous doing so might be for one's reputation, how does one ensure one's reputational status?

Here again, the value of uncertainty emerges. By stressing the *uncertainty* of the facts surrounding the safety of drugs such as Vioxx and the SSRIs, regulatory hesitations in removing the drug from the market seem prudent rather than negligent. Seen in this light, ambiguous or complex scientific phenomena carry a specific form of value: in that the more complex or contradictory a phenomenon, the harder it is to determine whether someone's interpretation of the data was correct or not.

The profitability of “manufactured uncertainty”

A growing number of analyses within the fields of human geography and science studies have scrutinized the usefulness of what Michaels calls “manufacturing uncertainty,” or the strategy of purposefully fostering scientific doubts over the safety of a given product (Michaels 2006). As Michaels and Proctor have noted, this strategy has been particularly endemic to the tobacco industry. “Doubt is our product,” a tobacco executive once noted on a marketing document, and for years large tobacco companies followed the mantra diligently, hiring scientists to contest the growing consensus linking smoking and cancer rates (Michaels 2006: 150), and engaging in “filibuster research” – Proctor’s term for the commissioning of ever more scientific studies to cast doubt on earlier ones (Proctor 2006: iv123). Although the tobacco firms eventually disbanded the strategy once scientific and epidemiological evidence proved too intractable, the tactic of manufactured uncertainty remains discernable in a number of different arenas, from court cases to regulatory inquiries.

For example, in his analysis of O.J. Simpson’s legal trial, Michael Lynch argues that Simpson’s defence lawyers approached the expert scientific testimonies advanced by the prosecution with the deftness of Latourian discourse analysts approaching a “black boxed” scientific fact, mobilising the scientific uncertainty implicit in the expert testimonies in order to foster reasonable doubt over Simpson’s guilt (Lynch 1998). Latour himself, as the sociologist Mariam Fraser points out, has raised concerns with the ramifications of his own illumination of the constructed nature of scientific facts, pointing out that in the case of global warming “dangerous extremists are using the very same argument of social construction to destroy hard-won evidence that could save our lives” (Latour 2004; quoted in Fraser 2006:47).

The usefulness and value of uncertainty has become a theme in literature on risk and regulation, where scholars have pointed out there is a contradiction between the proliferation of industries devoted to the containment of risk, and a rise in the manufacture of risk, where companies are increasingly attuned to the value of fostering risks which they are then employed to police (Ericson and Doyle 2004; Power 2004; Hutter and Power 2005). Scholars in this area have also drawn attention to contradictions within the introduction of the precautionary principle (see Levidow 2001; Majone 2002; Jasanoff 2006), noting that at times the adoption of the principle has been more useful for companies than for the constituencies the principle was intended to protect. By placing a premium on the need for regulatory caution, it has become more difficult at times for regulators to act swiftly on the removal of a product alleged to carry adverse effects. In the case of SSRIs, for example, the logic behind the principle has worked in favour of companies such as GSK which had already established the safety of their product in the eyes of regulators, for regulators seem to have interpreted their own duty as one of prudence in re-labelling SSRIs.

The literature supports my suggestion that a “a politics of conditionality” has emerged recently, where regulators and bureaucrats are increasingly sensitive to the political capital in appearing uncertain rather than authoritative about a given phenomena. With a slightly different normative position, this observation has parallels to work by Power, who has suggested that we should embrace the recent move towards a “politics of uncertainty,” for this would help foster “legitimacy for the possibility of failure,” and encourage recognition of the fact that “risks are ‘selected’ by institutions for a mixture of cultural and economic reasons” (Power 2004: 62).

In the following section, I explore the value of uncertainty during scientific debates by proposing three general characteristics of uncertainty: 1) Uncertainty, like certainty, is primarily a resource of those in positions of authority; 2) Contrary to expectations, the use of uncertainty often *consolidates*, rather than discredits, one's expert status, and 3) Uncertainty is performative: it creates a demand for resolutions the ambiguity it perpetuates, often strengthening the authority of those who have advanced a position of uncertainty to begin with.

Uncertainty, like certainty, is primarily a resource of those in positions of authority

At first glance, the suggestion in the heading above seems odd, particularly given that the use of uncertainty has typically been viewed as a resource for those who *lack* authority in struggles over power or resources. Pointing out, for example, that those in authority are less certain or knowledgeable than they purport has long been viewed as an influential political tactic (c.f. Taussig 1999; Coombe 2001). The use of strategic uncertainty therefore seems a questionable tactic for experts to adopt, for it seems only logical that no expert would willingly act in a way that might discredit his or her own expertise. Authority figures have more to lose, than to gain, by appearing uncertain or non-knowledgeable.²⁰

Related to this, individuals *without* authority often draw on scientific inconsistencies in order to mobilize support for a political cause, or to demand reparations following ecological or technical disasters. The case of Chernobyl offers an example of this. Unit Four of the Chernobyl reactor exploded on April 26, 1986, resulting in the largest nuclear catastrophe since the bombings of Nagasaki and

²⁰ I'm grateful to the discussions during a BIOS reading group session in March 2007, and particularly to comments by Chris Hamilton for this point.

Hiroshima. As the anthropologist Adriana Petryna writes, the scope of the casualties from the Chernobyl disaster remains widely debated to this day (2002). Petryna argues that in the indeterminate, transitional context of post-socialist Ukraine, “biology, scientific knowledge and suffering have become cultural resources through which citizens stake their claims for social equity in a harsh market environment” (Petryna 2002: 4). Although causal links between *high* doses of radiation and human biological effects were well-established, the biological effect of continued human exposure to *low* doses remains unknown. As a result of this indeterminacy, “assessments of injury are, by definition, open-ended and contestable” (2002: 17). Citizens exposed to radiation from Chernobyl became experts on their own physical suffering, mobilizing the scientific uncertainty surrounding the implications of radiation exposure as grounds for cementing their claim to state benefits.

A parallel to Petryna’s analysis is Veena Das’ ethnographic account of the ramifications of the Bhopal gas leak in India in 1984, for which legal contestations endure to this day (Das 1995). Though Union Carbide, now owned by the Dow Chemical Company, settled a civil compensation suit in 1989 by agreeing to pay Bhopal sufferers a lump sum of \$470 million, a criminal suit against Dow is still proceeding, and those living in proximity to the site are still being affected by contamination (see Hutter and Power 2005: 5). Das argues a common feature of the management of large-scale chemical or nuclear disasters is that “despite the pervasive uncertainty which surrounds such disasters – an uncertainty arising from the fact that the impact of toxic chemicals in the environment on human beings cannot be described in mechanistic terms – bureaucratic decisions are presented as if they were grounded in certainty” (1995: 142). A key strategy of toxic sufferers and their legal representatives has been to challenge bureaucratic definitions of illness

and safety by pointing out the scientific uncertainty that underpins their illusion of incontestability (Das 1995: 142).

The problem is, in both examples above, the claims of individuals sufferers are often fruitless unless one has access to a expert – physicians in the case of Chernobyl; lawyers in the case of Bhopal – to mediate and legitimate those claims. Typically, an individual requires scientific accreditation and expertise in order to cast doubt on the scientific certainty of others. If a lay individual tries to draw on scientific uncertainty in order to condemn a certain action as misguided, it is often assumed the individual simply lacks the requisite scientific understanding.

On the other hand, when a regulatory body such as the MHRA points to uncertain scientific data, or conflicting RCT results, as reasons for not acting, or as justification for having acted in a manner that later raises questions, their scientific expertise renders their decision legitimate and credible. Not only is the uncertainty of scientific experts understandable, the admission of uncertainty is often perceived as admirable. As the saying goes, he was big enough to admit his mistakes. As a general observation, uncertainty can not be drawn on as a resource as easily by lay individual as by experts. This leads to second aspect of uncertainty.

The use of uncertainty often consolidates one's expert status

At first glance, uncertainty seems to pre-empt or defer action. Particularly given how often uncertainty is framed in a negative light, or is linked with ambiguity, conflict and a lack of clear answers, it seems logical that uncertainty would have few productive uses, or that uncertainty contained little positive value. Uncertainty, however, is inherently active: *it creates a demand for solutions to the ambiguity which it perpetuates*. Not only does uncertainty create a demand for

resolutions, but often those who have suggested that particular situations are uncertain are best placed to resolve the very problems they have pointed out. This is because the expert who has cast doubt over a situation draws unique authority from the fact that only he or she can be said to know the full limits *of what is not known*. Just as the expert is uniquely placed to deploy her knowledge of what remains unknown, her pronouncements are effectively incontestable, for uncertainty, unlike expertise, is difficult to disprove. By fostering a situation of uncertainty which only she can resolve, the expert at times draws *more* authority from uncertainty than certainty.

Brian Balmer, a scholar of science and technology studies, raises a similar point in a draft article on how uncertainty served as a resource to British policymakers in building support for Britain's biological warfare programme in the period immediately following WWII. Balmer's analysis can be placed next to work by Lynch and Brian Wynne (Wynne and Irwin 2004) as one of the few studies within science and technology studies that have sought to interrogate the positive and productive uses of uncertainty (see also Jamieson 1996; Levidow 2001; Michael 2004). Previously, as Balmer notes, STS scholars have tended to view uncertainty in a negative light: as something which policymakers must struggle to avoid lest their competence be questioned. In the case, however, of Britain's early biological weapons programme the converse was true: policymakers stressed the magnitude of the uncertainty and the lack of knowledge surrounding the implications of biological warfare as a strategy for securing more funding for research and development.

This tactic, though, also posed risks for the policymakers who advanced it, for as Balmer stresses, the credible use of uncertainty by policymakers in the post-war period remained contingent on their prior positions of authority and expertise. In

other words, the strategic use of uncertainty is always linked to an individual's ability to express "legitimate doubt" (Balmer 2006). This point relates to the performative aspects of uncertainty.

Uncertainty is performative: it thrives on the inconsistencies it creates

Scholars in STS and feminist studies have long drawn on the notion of performativity: the idea that certain forms of language and activity instantiate phenomena which they seem at first to merely describe or foretell (c.f. Thrift 2005; Thrift 2007), or, to draw on Judith Butler's slightly different conception, the idea that discourse produces phenomena which it then constrains and regulates (Butler 2006). The concept of performativity has been particularly fruitful in the study of new technologies, where the subfield of the sociology of expectations has explored the ways that both hopeful and negative speculations play a productive role in the development of new technologies (Brown 2003; Hedgecoe and Martin 2003; Lentzos 2006; Novas 2006). It has also been useful in the field of political economy, where Michel Callon (1998) and Donald McKenzie (2006) have introduced the notion to the study of markets, exploring the extent to which economic science plays a role in creating the market activity which it alleges to simply describe.

Drawing on work by Thrift, sociologist Jakob Arnoldi has explored the value of uncertainty in an analysis of the financial derivatives market. He asserts that derivatives – secondary assets, such as options and futures, which derive their value from primary assets such as currency, commodities and stocks – are analytically interesting by virtue of the fact that they are sustained by the very uncertainty which they create: "Derivatives, as a technology, do not simply create risks or future uncertainties but in fact also use such uncertainties as a resource" (Arnoldi 2004: 23).

He furthermore draws parallels between derivatives and the usefulness of scientific uncertainty in general:

it seems that derivatives are just one example of an increasingly occurring, and highly paradoxical, phenomenon: the more indeterministic, contingent and even uncertain (and, as we shall see, virtual) scientific knowledge become, the bigger its influence on the world through the development of new technologies (Nowotny et al 2001: 185) – which again creates new uncertainties (Arnoldi, 2004: 25).

Building on this literature, I suggest the value of uncertainty lies in its opportunistic, promissory nature. When a situation is certain, it is finite: the horizon of possibility for future growth or exploitation appears to be constrained.²¹ When a situation is uncertain, it demands attention, debate, funding, and most crucially, experts to determine how the situation should be resolved.

Pointing out its performative value helps to illuminate why, in practice, the deployment of uncertainty tends to cement rather than to destabilize existent authority structures. A reason for this is that, as Balmer writes, the credibility of statements of uncertainty is contingent on the political and social authority of those advancing the statements.

To put it more starkly, drawing on scientific uncertainty as a resource is a useless strategy unless one has the institutional and symbolic capital to convince others that a situation is truly uncertain, rather than the opposite possibility: that an individual does not have an adequate grasp of the science involved. Chernobyl and Bhopal provide an illustration of this. I noted that the victims of these disasters attempted to draw on scientific uncertainty in order to contest bureaucratic assessments of risk and safety. The problem is, unless they had access to a professional mediator, such as a lawyer or a physician, to legitimate their claims, this

²¹ I am grateful to Nikolas Rose for help in formulating this point.

tactic was rarely efficacious. Often individuals must possess a degree of professional or political status in order to exploit scientific uncertainty. They require certainty in order to dispel it.

Problems of disclosure: Lessons from Enron, Vioxx and the SSRIs

The concept of strategic uncertainty is closely related to strategic ignorance, where, for example, pharmaceutical companies feign ignorance of the existence of unpublished clinical trials, as well as employ contradictory interpretations of trial results to productive purposes by selecting the most useful outcomes for publication in a journal article (Kendall and McGoe 2007). Industry bodies also appear to rely symbiotically on the use of uncertainty at regulatory bodies. As I suggested earlier with the concept of anti-strategies, even when companies do disclose all clinical trial results to a regulator, it is often the case that a regulator is structurally hampered from acting on that disclosure. Usefully, at the very point of a company's wilful or forced disclosure of data, a regulator adopts a strategic desire not to know.

This last point highlights what is problematic in the typical public and governmental responses to the recent series of drugs controversies. Following each controversy, calls are heard for more mandatory disclosure of trial results, for more public access to clinical trials and for less secrecy surrounding drugs regulation. Such calls ignore what is apparent from the analysis throughout this thesis of actions at the MHRA: information is useless if no one has the institutional authority or desire to act on it. As some have noted of the Enron controversy, problems surrounding corporate malfeasance are rarely attributable to situations of too little information. They are often, in a perverse and absurdly logical way – a problem of far too much (Macey 2003; Gladwell 2007).

As has been widely analysed in literature on securities regulation, the bankruptcies at companies such as Enron and Worldcom led to the passing of the Sarbanes-Oxley Act of 2002, the largest overhaul of corporate governance securities legislation since the Securities Exchange Act of 1934 (Heminway 2003; Paredes 2003). Observing this development, US health scholars have recently suggested that adopting a “Sarbanes-Oxley for Science” would help tackle the problem of the underreporting of clinical trials at places such as GlaxoSmithKline and Merck.

The suggestion was raised in a special issue of *Law and Contemporary Problems* (2006) which drew on the recent series of high-profile scandals involving the tobacco, chemical and pharmaceutical industries in order to examine the problem of “sequestered knowledge” within industry and regulatory bodies. The volume featured articles by scholars such as Sheila Jasanoff, and was novel for including two contributions from industry representatives – Scott Lassman, of the Pharmaceutical Research and Manufacturers of America, and James Conrad of American Chemistry Council, both of whom argued that existing US legislation was sufficient to ensure the disclosure of health and safety data.

The other articles in the volume were critical of disclosure laws which have led to, as Michaels notes in his introduction to the volume, regulatory inefficiencies in detecting problems surrounding Vioxx and the SSRIs. To address these inefficiencies, Michaels suggests the need to develop a “Sarbanes-Oxley for Science” which “would require corporations to designate a person responsible for reporting the results of studies undertaken by the firm” (Michaels 2006: 16). Michaels is alluding to section 302 of Sarbanes-Oxley, which stipulates that all CEOs and CFOs of public companies must sign a certification statement verifying the truthfulness of a company’s financial reports. Other major provisions of Sarbanes-Oxley are

encapsulated within section 404, which mandates companies to provide elaborate reports on their internal control systems as part of their annual reports. Section 404 has been heavily criticized by a number of observers, in part because the expense of complying with section 404 has far exceeded initial expectations, and been particularly onerous for small to mid-sized companies (Economist 2005).

The idea of a Sarbanes-Oxley for Science has some merit, particularly given the fact that, in the UK context, no pharmaceutical company or senior executives have ever been criminally penalized for the suppression of clinical trial data. But at least three criticisms can be made of Michaels' proposal. Firstly, he does not touch on the criticisms recently made of Sarbanes-Oxley within the sociology of risk and regulation, such as Power's argument that there is no proof that "reactively created certification and disclosure regimes" such as Sarbanes-Oxley have any capacity to create more regulatory compliance (Hutter and Power 2005: 6). Secondly, his equation of increased legislation with increased transparency ignores what is apparent from the discussion earlier of work by Barry and Simmel: a commitment to transparency often creates a simultaneous need for discretion (see also Hood and Heald 2006; Best 2007).

Often efforts to increase transparency through measures such as Sarbanes-Oxley have the unintended consequence of reinforcing the obscurity of corporate practices, in part because the onus to record transactions with "documentary precision, another label for the tick-box approach, is a feature of an institutional environment in which agents must develop strategies to avoid the possibility of blame" (Power 2005: 16; see also Barry 2006a; 2006b). These two points contribute to a third limitation of Michaels' proposal, which is its blindness to an institutional reality common to both Enron and GSK's handling of Seroxat. In both cases,

regulators, policymaker and expert advisors *did* have some access to information suggestive of fraudulent behaviour at these companies. They simply chose, or were unable, to act on it.

In their introduction to *Organizational Encounters with Risk* (2005), Hutter and Power touch on this, reiterating that in hindsight, it seems problems at Enron stemmed less from inadequate disclosure, but from institutional difficulties preventing the parties closest to Enron from interpreting signs of corporate failure even when signals were disclosed:

In the case of Enron, it was well known to many, especially to insiders, that the company and its reported growth were problematic and the collapse in retrospect was perhaps predictable, just as the fact of the September 11 attack on the US (if not the timing) is being reported in hindsight as predictable. But for the institutional actors at the time (financial analysts, accountants, FBI, CIA) it is necessary to understand the conditions under which such predictions and warnings could not be uttered, or if they were, could not be heard and processed (Hutter and Power 2005: 12).

Power reiterates this point in *Organized Uncertainty*, noting that in recent years financial scandals such as the bankruptcy at Barings bank have “come to be understood as management and governance failures rather than failures of analysis and information” (Power 2007: 10). In many ways, these insights are relevant to Foucault’s analysis in *History of Sexuality*, where he argues that, contrary to the idea that sexuality was a taboo discourse during the 18th, 19th, and 20th centuries, in reality sexual matters were spoken of excessively, with the most deviant or unaccepted practices often eliciting the most obsessive attention: “What is peculiar to modern societies is not that they consigned sex to a shadow existence, but that they dedicated themselves to speaking about it *ad infinitum*, while exploited it as *the* secret (Foucault 1990 (1976); quoted in Mookherjee 2006, see also Barry 2006).

Deleuze reiterates this point when he suggests, as I quoted earlier, that Foucault's greatest historical principle is the idea that "everything is always said in every age." Foucault was adamant that "behind the curtain there is nothing to see, but it was all the more important each time to define the curtain, or the base, since there was nothing hidden or beneath it" (Deleuze 2006 (1988): 47). Scholars have long noted that one of Foucault's contributions to political and social theory is his illumination of the way power is dispersed through society. Less attention has been paid, however, to how the visibility of power manages to constrain the possibilities of action, to the way people are often hampered by the very illusion of opportunity (Rose 1999), or how the seeming freedom to speak often leaves people "shorn of a vocabulary of protest" (Thrift 2005: 151).

Sheila Jasanoff's article is one of the few pieces in the recent issue of *Law and Contemporary Problems* focused on a Sarbanes Oxley for Science to recognize that disclosure alone does not ensure the possibility of action. In her article, which explores the ramifications of the concealment of scientific data from those "willing to criticize and able to make sense of it," Jasanoff criticizes GSK's handling of its Seroxat trials, noting that "the GSK case dramatized the problem of drug companies' not making negative results from clinical trials public, thereby skewing in a favourable direction, the information available on their products" (Jasanoff: 2006: 28). Despite the article's discussion of the need to combine disclosure practices with the means to enable individuals to comprehend what is disclosed, such as ensuring the scientific literacy to digest information, Jasanoff does not address a key question, which is the extent to which, as I have suggested of the SSRI controversy, regulators have been hampered structurally from *wanting to comprehend* disclosures.

GSK, Seroxat and problems of disclosure

As mentioned earlier, the appearance in 2004 of the document “Seroxat/Paxil Adolescent Depression – Position Piece on the phase III clinical studies”(see Figure1), suggested to many that GSK had intentionally withheld clinical trial data. To date, aside from settling out of court with Spitzer, GSK continues to maintain that it disclosed the results of its clinical trials to regulators in the UK and the US in a legal and timely manner, vociferously opposing those who have suggested otherwise. In January, 2007, Panorama aired the fourth programme in its series investigating the side-effects of SSRIs. The programme’s reporter, Shelley Joffre, argued that excerpts from the documents reproduced in Figure 2, such as the sentence “it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine,” suggested GSK may have intentionally suppressed clinical trial data (BBC 2007).

The following day, a GSK spokesperson denounced the statement as “defamatory” and added that GSK had considered legal action, but “there wouldn’t be much to gain from taking action against the BBC” (quoted in Barriaux 2007). Shortly following the Panorama programme, GSK posted a public statement on the BBC’s website, reiterating its rejection of Panorama’s allegations:

GSK conducted nine studies over eight years to examine the use of Seroxat in treating children, those under the age of 18, with depression and other psychiatric disorders as treatment options for these vulnerable patients are extremely limited. Results from these studies were documented and submitted to regulators in accordance with regulatory requirements. No suicides were reported in any of the nine paediatric trials conducted by GSK and when reviewed *individually* none of these trials were considered by GSK or independent investigators to show a clinically meaningful increase in the rate of suicidal thinking or attempted suicide. Only when all the data became available, at the end of the research programme, and were analyzed *together* was an increased rate of suicidal thinking or attempted suicide revealed in those paediatric patients taking Seroxat (GSK 2007).

From the statement above, it seems that it would be a fairly clear-cut process for regulators to determine whether GSK had acted lawfully in their regulatory submissions involving SSRI trials in children. Nine clinical trials is not an extensive number. Study 329, conducted in the United States during 1993-1996, involved less than 300 subjects – not a daunting number. Yet, more than four years after the MHRA first launched a criminal investigation into GSK’s submission of trial data, the inquiry is still inconclusive. During my interview with Woods, I asked how the investigation was going:

KW: This is a long and complex investigation which is nearing its conclusion. We have given a great deal of resources and efforts to doing this. I obviously can’t say much about it. Because we are at the moment waiting for analysis of council’s opinion. And the decision has not been made. As to whether this goes to court or not. But it has been a very large and intensive exercise from our point of view. I can tell you that we have obtained and examined over a million pages of documentation: that is a measure of the scale and the complexity and resources used in this case. And I can’t say anything more about it other than to say it is ongoing. And one reason why it is still ongoing is because of the scale of the work that it has entailed (LM interview with Kent Woods; January, 2007).²²

Though lengthy legal investigations are of course not unusual, particularly when it comes to untested areas of law, four and a half years does seem a long time to examine whether one company submitted sufficient RCT data as it has pertained to one drug. Unfortunately, there is little way to prove whether the lack of resolution has stemmed from insufficient resources, or, as Woods suggests, from the sheer complexity of the case, or as I have suggested, from the regulator’s interest in not revealing the possibility of its own inefficiencies.

²² The interview with Woods took place Jan. 31, 2007. Eight months later, Simon Gregor, the MHRA’s Director of Communications, confirmed the inquiry was still inconclusive: “Re: the GSK investigation, you have not missed any public announcements and the situation remains as it was when you met Prof Woods, that is that the investigation is ongoing” (MHRA 2007).

The point I wish to argue is that the sheer complexity of the case has itself been helpful in deterring attention from the possibility of negligence on the part of the regulator. The regulatory value of uncertainty was also discernable when I asked Woods about the GSK meta-analysis discussed earlier in Chapter 4, which revealed a six-fold increase in suicidal behaviour on the paroxetine arms of trials for depression in an adult population. GSK undertook the meta-analysis at the behest of FDA in the States. In May, 2006, they circulated a letter to healthcare practitioners indicating their own meta-analysis revealed the six-fold increase (Lenzer 2006). At the time, observers were shocked that both the MHRA and the FDA, both of which had had access to GSK's trial data for years, did not detect the increase earlier. I asked Woods why, in his view, the MHRA had not detected the increase earlier. He replied:

We are talking about events that typically were occurring at a frequency of 1% or less. And I think from memory – and this is from memory – the point estimate in the meta-analysis that Glaxo were describing was an incidence of .05% which went up to something like .33%. Now, firstly, the absolute figures make it much clearer what the scale of change is. And secondly, you have to ask the question, what is the contribution of random noise: in other words, six-fold tells you nothing about the statistical significance of that change. And it tells you nothing about the absolute scale of that change. If we're talking about event rates that were occurring at a frequency of less than half of 1%, you can see why meta-analyses may change slightly from time to time depending on what the events of importance of the analysis are. Are you talking about suicides? From memory there were no suicides in any of the trials. Are you talking about attempted suicides? Suicidal ideas? And whichever endpoint combination you use, you'll get a slightly different answer (LM interview with Kent Woods, January 2006).

Woods' comment is statistically correct, and at first glance seems a justifiable response. But the comment, and particularly his suggestion that the increased suicidality exhibited on the Seroxat arms of the trials may have been small enough to explain the MHRA's non-detection, raises a number of questions. While it is true that the increase is not large, it was significant enough for GlaxoSmithKline to circulate a

letter to healthcare practitioners advising them that a reanalysis of existent data had raised concerns with the company's own product:

In the analysis of adults with MMD (all ages) [mild-to-moderate depression], the frequency of suicidal behaviour was higher in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]. This difference was *statistically significant* (GSK 2006, emphases added).

Secondly, Woods suggests that with every new meta-analysis of individual RCTs, results can slightly differ, and this heterogeneity makes it difficult to detect risks. While this is certainly plausible, there are at least two objections. First, in order to licence a drug in the UK, two RCTs are generally required as proof of efficacy and safety. Logically, then, one should not be in a position to suggest that individual RCTs are, as Woods has suggested, often insufficient for detecting adverse effects. As Kendall said to me during a conversation on September 28, 2007, "If two trials are enough to establish the safety of drug, you can't turn around and say it's difficult to establish the risks of a drug based on just two trials."

Secondly, Woods' comment suggests that the MHRA took every means necessary to scrutinize all available data. During the MHRA's 2003-2004 expert working group's investigation into the safety of SSRIs, the working group *did* write to all companies requesting clinical trial data related to suicidal events. Companies were asked to provide a variety of data, including summaries of all clinical trials, whether published or not, as well as case narratives of any suicides that occurred during trials. What the working group did *not* examine, however, is individual patient data from the clinical trials, despite the fact that, as the experts I have spoken to have reiterated to me, the analysis of individual data is vital for determining things such as how reliably endpoints have been recorded. After having analysed the *summary*

reports provided by GSK, and not all available individual data, the MHRA expert working group concluded:

These data show no conclusive evidence that adult patients exposed to paroxetine are at increased risk of suicidal events compared with patients exposed to either placebo or another active drug in any of the indications investigated. *However, the data are consistent with the possibility of an increased risk of suicidal events in patients with depression exposed to paroxetine compared to placebo* (MHRA 2004: 82, emphasis added):

The MHRA's report went on to note that:

The meta-analysis has been restricted to data provided from trials conducted by the MA Holder [GSK], and has not included any data from other randomised trials conducted by other groups or published studies. *Consequently it is not a formal meta-analysis of all available data.* Whilst the results provide no clear evidence of an increased risk, the range of risk ratios included within the 95% confidence intervals are consistent with the possibility of a small increased risk of suicidal events for patients exposed to paroxetine compared with placebo (MHRA 2004: 82-83, emphases added).

Despite the fact that the 2003-2004 working group was the sixth time the MHRA formally convened a committee to investigate the possibility of suicidal risk, the working group did not scrutinize the individual patient data held by GSK, nor did it attempt a more comprehensive meta-analysis when initial findings revealed the possibility of a small increase of suicidal events, nor did it direct, as the FDA later did, GSK to undertake another meta-analysis of its own data. As I noted in Chapter 4, this strategy of non-detection – whether deliberate or not; and whether morally acceptable or not – has been in many ways been rational: it is logical that staff did not search for what they did not want to find, or be forced to act on.

Conclusions

Comments such as the one above from Woods illuminate what is problematic with the common reaction to the realization that companies have withheld clinical

trial data from government regulators and from the public. Observers assume that disclosure alone will lead to regulatory action, and fail to grasp, as Hutter and Power note of Enron and 9/11, the organizational conditions which make it difficult for someone involved with an inquiry to process the information that *is* disclosed. Outside a few observers, many have failed to recognize the nuanced relationship between disclosure and action. They have failed to grasp the reciprocity, as Barry describes, between transparency and discretion.

In an article, for example, about government secrecy and the amount of information deemed classified by US securities agencies, Peter Galison, despite a provocative analysis of the perils of “removing knowledge” (2004) from public consumption, seems to miss this relationship. In the article, Galison suggests we must pay more attention to “antiepistemologies” at root of theories of knowledge: “epistemology asks how knowledge can be uncovered and secured. Antiepistemology asks how knowledge can be covered and obscured. Classification, the antiepistemology par excellence, is the art of nontransmission” (2004: 237).

Galison’s weakness in the article is his distinction between classified knowledge, or secret knowledge that leads to the production of ignorance; and open knowledge, knowledge which is unclassified and therefore, he suggests, amenable to scrutiny. In truth, there is no simple, linear relationship between declassification and action. At times disclosure might even render it *harder* to act, for disclosures often compound the difficulties – whether feigned or real – in interpreting information. As Foucault reminds us, often the most taboo topics are those that are spoken of most often.

The insight echoes a comment by Tocqueville (1848), who struggled to grasp the oddly placating, rather than incendiary, influence of the free press in America.

When something is free “there is no need to struggle for it...because of the large number of publications, readers become desensitized: they are not ‘affected by...deep passions. Because of the cacophony of opinions, they take note of the contents only with a certain detached indifference” (Tocqueville 1848, quoted in Offe 2005). Perversely, through a strategy of “open secrets,” individuals are often *constrained* from acting, paralysed by the volume of the information which appears before them.

Conclusions: The value of ignorance and uncertainty within cultures of objectivity

One of the difficulties in charting recent debates over the safety of SSRIs has been the dynamism of the object of study. I first became interested in questions of SSRI safety in the early months of 2004, when I read media coverage of FDA hearings in the United States where dozens of parents testified to their belief that SSRIs had precipitated the deaths of their children. After watching the hearings, I wrote a short PhD proposal which suggested that the parents and family members of children who had died while on SSRIs might have relevance to concepts of “biosociality” (Rabinow 1996) and “biological citizenship” (Rose and Novas 2005):

It is possible that the collective of parents in court, contesting the construction and medicalization of their children’s shared afflictions might...act as a counterhegemonic weight: A biosocial group drawing on the commonality of their children’s biological identities in the negotiation of social and human rights (LM PhD proposal).

Although the subsequent thesis has of course changed since this initial proposal, my interest in the topic, and the questions it raises about the ability of individuals to contest authoritative pronouncements on the boundaries of health and illness, and the terms under which people are able to participate in the “politics of life itself” (Rose 2006), has not. Neither have some of the preconceptions with which I approached the research.

I remember feeling considerable sadness when I read the testimonies of parents in court, and shock that they had no access to clinical trial data that related to their children’s treatments. This feeling of sadness and anger has returned every time I have stumbled across a new document online which suggests that companies have deliberately buried data. And that has been many times. Leaked documents similar to

the GSK document in Figure 2 are abundant on the Internet. Their legal status may be dubious, but their emotive strength is not. In reading them, I still find it hard to believe company staff, when viewing trial results that revealed a lack of efficacy for their drug, strategically planned how “to effectively manage the dissemination of these data in order to minimise any potential negative commercial impact” (GSK 1998; see Figure 2). It remains harder still to believe that no company has faced punitive measures by UK regulators for their actions.

Combined with feelings of sadness has been the need to try and view my data with as open a mind as possible. Although personally I believe that objectivity is neither possible, nor necessarily desirable, when it comes to social science research, I also think it is necessary to strive after realistic accounts of events, mending one’s position when new facts – whether derived from the anecdotal, narrative reports from parents or psychiatrists, or from RCT or epidemiological data – appear to suggest a prior position was wrong or incomplete. One must be particularly sensitive to this need when analysing a controversy that remains unresolved, and where new studies and media articles on the topic at hand continue to appear almost daily.

I was faced with this difficulty in September 2007, when the media announced the publication of a study from the United States that had captured headlines around the world. Appearing in the September issue of the *American Journal of Psychiatry*, the study, entitled “early evidence on the effects of regulators’ suicidality warnings on SSRI prescriptions in suicide in children and adolescents,” suggested that warning labels issued by US and European regulatory agencies had contributed to an increase in suicides in children and adolescents, because fewer children were being prescribed the drugs (Gibbons, Brown et al. 2007).

Drawing on epidemiological data, the study noted that the number of suicides among Americans aged younger than 19 years was 14% higher in 2004, the year the FDA stipulated SSRIs must carry a black box warning indicating suicidal risk, than it was in 2003. During that period, prescriptions of SSRIs fell by 22% in this age group (Dyer 2007; Gibbons, Brown et al. 2007).

The study led Thomas Insel, director of the US National Institute of Mental Health, to suggest “we may have inadvertently created a problem by putting a [FDA] ‘black box’ warning on medications that were useful. If the drugs were doing more harm than good, then the reduction in prescription rates should mean the risk of suicide should go way down, and hasn’t gone down at all – it has gone up” (quoted in Vedantam 2007).

The Internet started buzzing with the story, with many offering unequivocal comments on the study. A blog at “*Drugwonks.com*,” the weblog of the Center for Medicine in the Public Interest (CMPI), a forum offering “rigorous and compelling research on the most critical issues affecting current drug policy,” praised the study for confirming that observers such as David Healy had been wrong in their assessment, adding the question “where will Healy, David Graham and the rest go to wash the blood off their hands?” (Drugwonks.com; last accessed September 14).

Others were more tempered. An article in the *New York Times* noted that Gibbons’ study was being heavily questioned by experts across the United States, who noted “there doesn’t seem to be any evidence of a statistically significant association between suicide rates and prescriptions rates provided in the paper” (Ted Haves, a professor of biostatistics at the University of Pennsylvania, quoted in Berenson and Carey 2007). Other experts suggested the study simply reiterates that suicide trends are difficult to understand – driven as they are by factors such as

worsening depression levels, economic factors such as job loss and increased access to guns (Berenson and Carey 2007).

It was Healy himself who emailed to call my attention to the web log at *Drugwonks.com*. As I noted earlier, many have questioned Healy's behaviour in raising concerns over SSRIs, suggesting he "has gone too far," or that the manner in which he voiced his objections helps to explain why he has been disparaged both in the press and by peers for his comments on SSRIs.

Others suggest he has acted courageously in voicing his opinion on SSRIs – one that was later validated by RCT evidence – when the majority of observers sided against him. In reading comments such as the one above, suggesting Healy should have numerous deaths on his conscience, my own view is two-fold: First, I think the tone of the comment on *Drugwonks.com* helps to explain the defensiveness with which Healy has at times asserted his own position, attacking others before they can attack him. Secondly, I think the vilification of Healy supports my suggestion of the moral authority of objectivity. The very fact that Healy's manner – impassioned, antagonistic, polemical – has been viewed with such criticism, supports my argument that unless one adopts a language of impartiality in voicing objections, one risks one's professional status, as well as the ability to convince one's peers.

Healy's main argument – that RCT data reveals an increased risk of suicidal behaviour of those randomized to SSRIs – has now been accepted according to the trial data on which the FDA called for warning labels on SSRIs. What remains unclear, however, is whether, in advising patients of this increased risk, the MHRA and the FDA have inadvertently contributed to fewer patients seeking treatments that might have saved their lives. As Insel, director of the NIMH said, "you focus on that very tiny number of kids who may be at greater risk when they are treated and you

ignore the very large benefit that might accrue to the other 99.9%” (quoted in Vedantam 2007).

This final dilemma is a difficulty I have encountered often throughout my research. On countless occasions, at parties, during conference talks, I have been asked to summarize my findings on the safety of SSRIs. People want to know: do they or don't they lead to suicide? To explain that, after numerous interviews with psychiatrists and policymakers, after months poring through clinical trial data, after years of research and writing, I still had no conclusive findings either way (the RCT data says yes; the epidemiological data suggests no) was generally met with disappointment and occasionally the expression of doubt for a) my own personal research competency or b) the futility of sociological research in general.

I quickly found the need to come up with one-line sentences that could justify my own lack of conclusions. Somewhat inadvertently, these stock responses have been useful in formulating the theoretical suggestions of the thesis. The three stock responses are as follows:

1) The very fact that most of the experts I spoke with had no legal access to clinical trial data that could offer them a better understand of the risks and benefits of SSRIs is a finding in itself.

2) Rather than solely being a detriment, it appears that for some the uncertainty and lack of conclusions regarding the safety of SSRIs have in fact been a resource. Whether they are conscious of it or not, scientific uncertainty has been helpful to regulators in absolving them of the failure to act quickly in publicly disclosing the adverse effects of SSRIs when they first learned of them.

3) Extrapolating from the SSRI controversy, I suggest that forms of “strategic ignorance” are valuable to regulators, policymaker and manufacturers in seeking to justify their own mistakes, or to absolve their culpability in actions later seen as questionable.

The response of friends, colleagues and family members when I have mentioned these suggestions has itself been illuminating. I have found that regarding the first point, individuals are generally shocked, and rather sceptical when I insist that, surprisingly, the problem of access to trial data is not more widely discussed or frowned upon in medicine.

Regarding the second point, colleagues have generally been receptive, alerting me to literature from scholars such as Brian Wynne, Mike Michael and others on the value of uncertainty, which helped to build the corpus I had been developing from work by Power, Thrift and others.

Regarding my last suggestion of the value of ignorance, I have found academics have routinely responded with scepticism, whereas friends and family members who work in finance and industry have either seen the idea as banal and unsurprising. Or they have taken out pens and jotted down notes. One family member, employed as the CEO of a Canadian telecommunications company, later emailed to tell me that his company's legal team has started drawing on the idea of "SI" (as they had shortened the phrase "strategic ignorance") to describe the actions of a rival company they were engaged in litigation with.

The email brought to mind Thrift's observation of how managerial discourses within capitalism routinely adopt even critical sentiments from academe and exploit them for guidance and inspiration. As Thrift writes, a key characteristic of the managerial discourses within soft capitalism is that "there is no theory that is not, or can not, be made complicit" (Thrift 2005).

At low points during the completion of this thesis I have been worried that after three and a half years of research into what began as an inquiry into the corporate structures that prevent access to clinical trial data, I may have helped to develop little

more than a handy acronym, “SI,” something that could help corporate players better strategize how to draw attention to their rivals’ illicit or incompetent actions and divert attention from their own. On more optimistic days, though, I am confident the thesis offers more than simply business tips. A brief examination of my main findings helps to support this view.

Ignorance, uncertainty and the politics of objectivity

In the first part of the thesis, drawing on the House of Commons Health Select Committee’s inquiry into the influence of the pharmaceutical industry on health policy, I examined the structure of drugs regulation in the UK, introducing the factors, such as funding structure, commercial confidence laws, and concerns over reputational status that have made it difficult for the MHRA to act quickly on suggestions of adverse effects. I noted that the Health Select Committee was fairly outspoken in its criticisms of drug regulation, and particularly of the MHRA’s handling of the SSRI controversy. The committee stated the following, for example, in its final report:

The antidepressant controversy is not yet over, but it has already had a profound effect on the shape of drug regulation as well as on the reputation of the industry...We look forward to hearing the results of the investigation into the withholding of information by the manufacturers of Seroxat, currently underway by the MHRA (HOCa 2005).

The first part of the Committee’s statement can not be said to be accurate. The SSRI controversy has not had a profound impact on the shape of drug regulation in the UK. Drug regulation has hardly changed at all. The Labour government has chosen to mostly disregard the Health Select Committee’s 48 recommendations, leaving the clinicians I spoke with feeling frustrated by the lack of government attention to problems within drug licensing and post-market surveillance. With

regard to the second part of the statement above: “We look forward to hearing the results of the [MHRA] investigation into the withholding of information by the manufacturers of Seroxat.” Well. With this anticipation, they are hardly alone.

Following an examination of the structure of UK drug regulation, I introduced the debates over the safety of SSRIs, drawing on literature from RCTs, as well as interviews with individuals close to the controversy. Rather than simply ask whether the MHRA has been incompetent in its detection of the adverse effects of SSRIs, I focused instead on the factors that have rendered incompetence a possible, and even attractive strategy when faced with multiple funding and reputational pressures.

The themes developed in this chapter are intended to complement work by Vaughan, Turner and Power on the reasons why an institution might be pressured to avoid processing the very information they are mandated to detect. I am *not* claiming to have offered a comprehensive empirical case study of organizational behaviour or regulatory (non)compliance. I am not purporting to have offered a case-study of the type employed by Hutter (2001), nor has that been an aim. The goal has been instead to develop a preliminary typology of the uses of ignorance in the political economy of drug regulation; to explore the situations where, as Luhmann writes, ignorance, and not knowledge, is often the most important resource of action (19998: 94).

I think there remain some shortcomings in the typology of ignorance I have developed: weaknesses that do not defeat the importance of the ideas, but which suggest avenues for future inquiries. The main weakness is the difficulty in assessing whether the adoption of strategic ignorance is a deliberate tactic, or an unconscious side-effect of institutional pressures. This limitation has stemmed in part from methodological obstacles, the largest of which is that I was not granted more interviews with MHRA regulators. In a number of instances, such as 1) the denial by

pharmaceutical companies of the existence of unpublished clinical trial data on SSRI use in a paediatric population, later exposed as a deception when the MHRA posted additional data on its website, and 2) the threatened prosecution of Brook when he asked permission to publicly disclose data on dosing levels, it appears evident that neither the pharmaceutical industry, nor the MHRA, were acting in the interest of patients. But whether these decisions were made a result of premeditated deception, or incompetence, remains hard to prove.

Even if I had interviewed more regulators, the extent to which actors themselves are unable to articulate the institutional pressures they are subject to makes it unlikely that I would have been able to shed more light on the *motives* of individuals for acting in certain ways. Far from being a unique limitation of my thesis, the failure to elucidate individual motives illuminates yet again one of the largest challenges of sociological research in general: the difficulty in discerning meaning from the representations and narratives people tell of their own actions (Rabinow 1986; Crapanzano 1990).

The problem of accessing and representing motives is also pertinent to a second contribution of my thesis, which is my suggestion of “methodological mimesis,” or the idea that individuals must phrase their dissent through a use of the methodologies they seek to oppose. I have suggested that as a consequence of this tendency, the very methods one seeks to contest are often perversely strengthened in practice. In the case of RCTs, for example, while individual RCTs may be criticized, RCTs as a methodology retain their status as the most valued form of experimentation to determine a treatment’s efficacy and safety.

I further developed this point in Chapter Six, which explores how the moral authority of objectivity makes it difficult for practitioners to voice dissenting

opinions during debates over SSRIs unless they have access to RCT data to support their views. The need to refer to RCT data in order to support one's argument illuminates just how crucial are political struggles over access to RCT evidence. Access to data should not be viewed, as many do, as a mere marginal or academic concern within medicine. As Tim Kendall argued, insufficient access to data should be seen as a fundamental problem threatening the "evidential basis of contemporary medicine" (Kendall and McGoeys 2007: 140).

Although there have been some optimistic developments recently, such as the stance taken by journals such as *JAMA* (Kendall and McGoeys 2007), the problem of lack of access to data remains underappreciated. The problem becomes even more intractable when one considers my final argument, which is that disclosure alone will not ensure regulatory action when trial data does reveal previously undetected side-effects.

In the last part of the thesis, I argued that the cases of Vioxx and the SSRIs illuminated the value of uncertainty to both regulators and companies in absolving their mistakes when, as a result of institutional pressures, they are forced to act in a manner contrary to public expectations of how they should act. One of the things I stressed that prior positions of authority have an influence on one's ability to draw on both certainty and uncertainty as political and professional resources. Despite what at first seems most logical, which is that uncertainty would be a threat to one's expert status, in practice the use of uncertainty tends to strengthen, rather than discredit one's authority, because the expert who insists that a situation is uncertain is often the only one who can pronounce on the limits of what is unknown.

This last point is pertinent to my discussion of the politics of objectivity in medicine. I have argued that the authority of objectivity makes it hard to express

dissent within medicine unless one restricts one's objections to the sphere of numbers. Evidence-based medicine, by narrowing the scope of contestation to the realm of scientific data, has been an *anti-political* movement – diminishing the authority of clinicians and patients to express “legitimate doubt” (Balmer) over a decision or action unless they have the means to defend their opinion by drawing on RCT data. It is the *anti-political*, versus political character of EBM that leads me to question observers such as Holmes who deride EBM for being an overly political, even “fascist” movement.

Rose has suggested that “by designating something ‘political’ you are seeking to designate that aspect of existence as something that is amenable to struggle and contestation...to call something political, it seems to me, is a performative act: it is trying to pull something into the field of contestation, just as to call some question ‘technical’ is to try to remove it from the field of contestation” (Rose, quoted in Gane 2004: 182). In line with that sentiment, this thesis has explored the factors that have led EBM, in contrast to the suggestions of its most ardent critics, to have an anti-political effect on practitioners.

One such factor is the moral salience commanded by objective styles of reasoning. This salience is particularly crucial in debates over drugs, where whoever manages to appear the most non-partisan often has the greatest legitimacy. The authority commanded by those who appear the most objective in a given situation relates to my argument that a strategic use of both ignorance and uncertainty has been valuable to regulators and manufacturers. I have suggested that the ability to draw on uncertainty is often contingent on one's prior position of authority. Extrapolating from this, it becomes apparent that strategies of uncertainty and ignorance are integrally connected to the moral authority of objectivity in medicine,

because one's status as a detached, objective expert helps to confer credibility when one seeks to express "legitimate doubt" about the certainty or uncertainty of a situation.

In order to harness the value of uncertainty, one must first mobilize objectivity; one must appear divested of personal interest in the outcome of a situation at hand. The effective use of ignorance and uncertainty is contingent on the ability to appear as though one has nothing personal or political to gain by pointing out that a particular decision or course of action is uncertain. Below, I suggest this point illuminates a number of shortcomings with previous analyses of the value of uncertainty.

The political value of unmanageable risks

Scholars of bureaucracy have pointed out that the anonymity of bureaucratic decision-making carries a form of political capital: it renders personal accountability difficult, as often the perpetrators of either mistakes or wilful acts of deception can not be identified. As Hannah Arendt writes in the essay "On Violence":

Today we ought to add the latest and perhaps most formidable form of such domination: bureaucracy...the rule of intricate systems of bureaus in which no men, neither one nor the best, neither the few nor the many, can be held responsible. (If, in accord with traditional political thought, we identify tyranny as government that is not held to give account of itself, rule by Nobody is clearly the most tyrannical of all, since there is no one left who could even be asked to answer for what is being done) (1969: 38).

Arendt's statement is relevant, as a point of contrast, to Power's recent suggestion (2004; 2007) that we should adopt a new "politics of uncertainty." In this politics, "expert fallibility" would be met with greater public understanding and not immediate reprimands. Fallibility would serve as "a basis for trust in [experts] rather than its opposite" (Power 2004: 63). Power stresses that the new politics of

uncertainty would not usher a return to unaccountable expertise, but would instead help to ensure a measured and sensitive response when decisions “turn out in retrospect to have been wrong, though honestly and reasonably made” (Power 2004: 63).

Power’s proposal has a number of benefits. In particular, he raises the idea that it would be ethically responsible, as well as more efficient, for regulators to abandon the illusion of their own omnipotent expertise. Rather than be constrained by the demands of appearing more certain than they are, regulators would have more professional freedom to call attention to their own mistakes, something that might have been useful during the SSRI controversy. Despite, however, the insightfulness of this point, I think that calling for a politics of uncertainty is premature until the *current* politics of uncertainty and conditionality is better understood. In particular, we need, firstly, to better understand how those in authority stand to gain by *purposefully calling attention to their own limitations*. Secondly, we need to gauge to what extent those in authority are aware of this resource, and have been profiting from it for years.

Paying more attention to the usefulness of ignorance and uncertainty may help to nuance a long-held notion in studies of regulation and risk, which is that there is political value and capital in *maintaining an illusion of manageability and control*. As is often quoted from Douglas and Wildavsky: “Can we know the risk we face, now or in the future? No we can not: but yes, we must act as if we do” (Douglas and Wildavsky 1980: 1).

In my study, the opposite has been true: the illusion of manageability was *not* sought after by expert figures. Instead, those in authority, from the MHRA to companies such as GSK, stressed the unmanageable and fluctuating nature of drug

regulation, and the unknowable character of a drug's performance outside the boundaries of a clinical trial, in order to justify previous regulatory actions.

Logically, one would assume that emphasizing the chaos, instability or uncertainty of a phenomena would be the *least* advisable course of action for individuals in authority, whether they are elected officials, regulators or scientists. This logic, however, ignores the performative nature of uncertainty: the way uncertainty fosters a demand for resolution to its own inconsistencies.

Indisputably, there are many situations where expert authorities must maintain, as Douglas and Wildavsky note, the illusion of manageability. But equally, the converse is also true. If people truly believe a situation is entirely manageable, then those in authority have inadvertently surrendered a key resource: which is the insistence that they alone are capable of resolving the uncertainties in a situation. Seen in this light, the *illusion of unmanageability* becomes just as powerful a resource as the *illusion of control*.

In my examination of debates over the safety of SSRIs, there have been few clear answers. Regarding the question of whether SSRIs contribute to suicide, regulators, practitioners and patients remain divided over the risk and benefit of the drugs. On the question of whether companies have deliberately suppressed SSRI clinical trial data, there has been, as the ongoing MHRA investigation of GSK indicates, no clear evidence as to whether companies committed fraud. Despite the lack of a legal consensus, most of my informants are convinced that companies have deliberately withheld data, and that a factor compounding and facilitating industry malfeasance had been the inability of regulators to detect and punish such behaviour. Unfortunately, in my view, suggestions for how to address this problem, such as a Sarbanes Oxley for Science, may only compound the problem.

One of my few clear findings has been something I have come to think of as the “consolations of chaos”, or the realization that negative virtues such as ignorance and uncertainty often have productive purposes for those who have the institutional and reputational capital to exploit them effectively. In the end, that hardly feels like much of a consolation at all.

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